IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: U.S. Patent No. 6,676,929
Issued: January 13, 2004
To: Thomas J. McMurry et al.
For: Diagnostic Imaging Contrast Agents with Extended Blood Retention

Office of Patent Legal Administration
Mail Stop Hatch-Waxman PTE
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

TRANSMITTAL LETTER FOR APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Attached in triplicate is an Application for Extension of Patent Term Under 35 U.S.C. § 156 of U.S. Patent No.6,676,929, with accompanying Appendices I-IV. Pursuant to 37 C.F.R. § 1.20(j), the prescribed fee of $1,120.00 for receiving and acting upon the application is enclosed. Please apply all other charges or credits to Deposit Account No. 06-1050.

The undersigned counsel may be reached in our Twin Cities office by telephone at (612) 335-5070. All correspondence should be directed to our address given below.

Respectfully submitted,

Date: 2/2/09

Teresa Lavoie
Reg. No. 42,782

Fish & Richardson P.C.
60 South Sixth Street , 3300 RBC Plaza
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

Enclosures: Three copies of Application for Extension of Patent Term Under 35 U.S.C. § 156 (incl. Appendices I-IV). Two additional copies of this transmittal letter. Check for $1,120.00. Return Receipt Postcard.

CERTIFICATE OF DELIVERY BY HAND

I hereby certify that this correspondence is being delivered by hand on the date indicated below and is addressed to the U.S. Patent and Trademark Office, Office of Patent Legal Administration, Mail Stop Hatch-Waxman PTE, Room MDW 7D55, 600 Dulany Street (Madison Building), Alexandria, VA 22314

2/2/09
Date of Delivery

Joseph Taylor
Signature

Joseph Taylor
Typed or Printed Name of Person Signing Certificate

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patentee : Thomas J. McMurry et al.
Patent No. : 6,676,929
Issue Date : January 13, 2004
Serial No. : 10/034,522
Filed : December 20, 2001
Title : Diagnostic Imaging Contrast Agents with Extended Blood Retention

Office of Patent Legal Administration
Mail Stop Hatch-Waxman PTE
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

I. Applicant, Epix Pharmaceuticals, Inc., represents that it is the owner of record of the entire right, title and interest in and to United States Patent No. 6,676,929, issued on January 13, 2004, identified above by virtue of:

A chain of title from the inventors of the above-referenced patent application to the current assignee as shown below:

1. From Thomas J. McMurry, Hironao Sijiki, Daniel M. Scott, and Randall B. Lauffer to METASYN, INC. The document was recorded in the Patent and Trademark Office at Reel 014038, Frame 0057 on October 09, 2003.

2. From METASYN, INC. to EPIX MEDICAL, INC. The document was recorded in the Patent and Trademark Office at Reel 014038, Frame 0039 on October 09, 2003.

3. From Thomas J. McMurry, Hironao Sijiki, Daniel M. Scott, and Randall B. Lauffer to EPIX MEDICAL, INC. The document was recorded in the Patent and Trademark Office at Reel 014177, Frame 0338 on December 05, 2003.

4. From EPIX MEDICAL, INC. to SCHERING AKTIENGESELLSCHAFT. The document was recorded in the Patent and Trademark Office at Reel 013745, Frame 0964 on June 18, 2003.

5. From EPIX MEDICAL, INC. to EPIX PHARMACEUTICALS, INC. The document was recorded in the Patent and Trademark Office at Reel 015962, Frame 0734 on March 29, 2005.

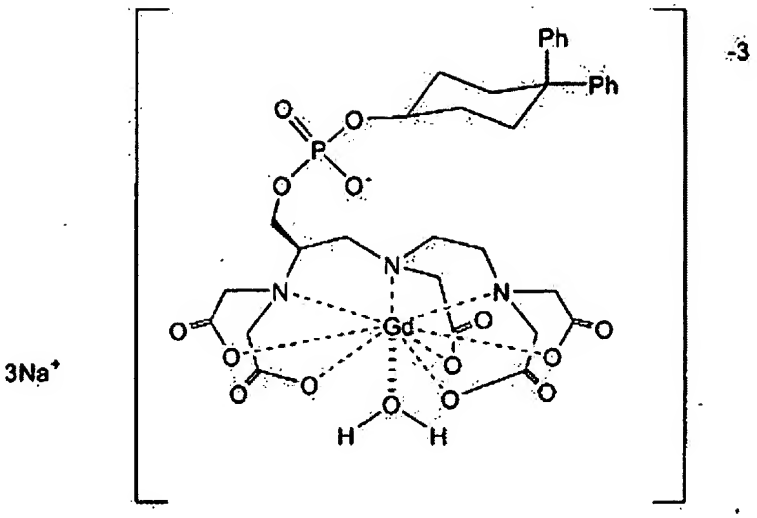
6. From SCHERING AKTIENGESELLSCHAFT to EPIX PHARMACEUTICALS, INC. The document was recorded in the Patent and Trademark Office at Reel 018535, Frame 0079 on November 14, 2006.

A certified copy of the chain of title is attached as **Appendix I.**

II. Epix Pharmaceuticals, Inc. submits this Application for Extension of Patent Term under 35 U. S. C. § 156 by providing the following information as required by 37 C. F. R. § 1.710 through 1.785. Applicant is filing this Patent Term Extension application in conjunction with another such application for a different patent. Pursuant to 37 C.F.R. § 1.785(b) and (e) and MPEP § 2761, applicant will elect which patent to extend (and expressly withdraw the application for the other patent) upon receipt of a final determination. For convenience, the information contained in this application will be presented in a format which follows the requirements of Section 1.740 of Title 37 of the Code of Federal Regulations.

1. The complete identification of the approved product VASOVIST is as follows:

VASOVIST (gadofosveset trisodium) Injection is a sterile, nonpyrogenic, formulation of a stable gadolinium diethylenetriaminepentaacetic acid (GdDTPA) chelate derivatized with a diphenylcyclohexylphosphate group. Gadofosveset trisodium is described chemically as trisodium-{(2-(R)-[(4,4-diphenylcyclohexyl) phosphonooxymethyl]-diethylenetriaminepentaacetato)(aquo) gadolinium(III). The empirical formula is $C_{33}H_{40}GdN_3Na_3O_{15}P$, and the molecular weight is 975.88 g/mol. The structural formula of gadofosveset trisodium is set forth below.



Each mL of VASOVIST Injection contains 244 mg of gadofosveset trisodium (0.25 mmol), 0.27 mg of fosveset, and water for injection.

2. The regulatory review has taken place under § 505 of the Food Drug & Cosmetic Act.

3. The product received permission for commercial marketing or use under § 505 of the Food Drug & Cosmetic Act on December 22, 2008.

4. The active ingredient in the approved product is gadofosveset trisodium, which is indicated for use as a contrast agent in magnetic resonance angiography (MRA) to evaluate aortic occlusive disease (AIOD) in adults with known or suspected peripheral vascular disease. Gadofosveset trisodium had not been previously approved for commercial marketing or use under the Food Drug & Cosmetic Act(either alone or in combination with other active ingredients) before the approval of VASOVIST on December 22, 2008.

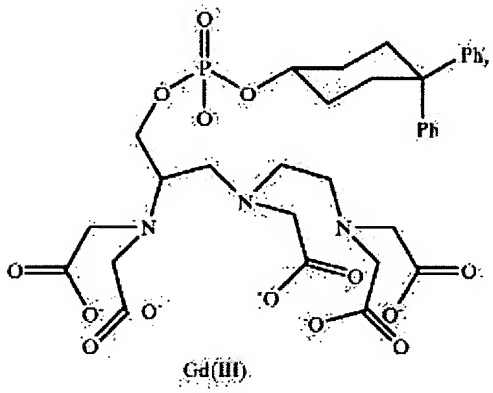
5. This application is being timely submitted within the sixty (60) day period permitted for submission pursuant to 35 U.S.C § 156 (d)(1) and 37 C. F. R. § 1.720 (f). The last day on which this application could be submitted is February 19, 2009.

6. The U.S. Patent for which an extension is being sought is U.S. Patent No. 6,676,929. The names of the inventors are Thomas J. McMurry, Hironao Sijiki, Daniel M. Scott and Randall B. Lauffer. U.S. Patent No. 6,676,929 issued on January 13, 2004, is subject to 114 days of patent term adjustment and will expire on May 26, 2015.[1]

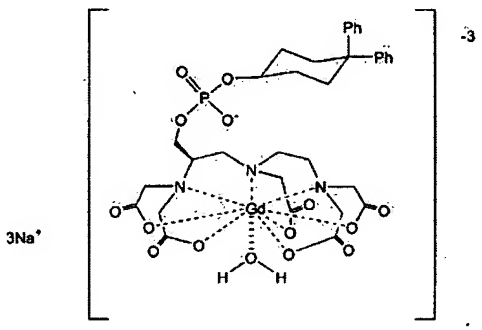
7. A copy of U.S. Patent No. 6,676,929 is attached hereto in **Appendix II**.

8. A copy of the Certificate of Correction and Maintenance Fee Statement for U.S. Patent No. 6,676,929 are attached hereto as **Appendix III**. No maintenance fee is currently due on this patent.

9. U.S. Patent No. 6,676,929 covers the approved product VASOVIST in Claim Numbers 2, 9 and 10.

Claims of U.S. Patent No. 6,676,929	**Claim reads on VASOVIST**
Claim 2. A diagnostic imaging contrast agent having the following structure:  wherein Ph=phenyl.	Claim 2 covers the product VASOVIST by reciting a diagnostic imaging contrast agent having a certain structure. Per the description in II 1. above, VASOVIST is a gadolinium-based contrast agent for use in magnetic resonance angiography (MRA). The active ingredient in VASOVIST is gadofosveset trisodium. The chemical structure of gadofosveset trisodium is set forth below:

[1] U.S. Patent No. 6,676,929 is entitled to at least a term of 20 years from its earliest effective filing date of February 1, 1995. It would therefore expire on February 1, 2015, but the PTO determined it was entitled to a Patent Term Adjustment of 114 days, yielding an expiration date of May 26, 2015.

	
Claim 9. A pharmaceutical composition comprising a diagnostic imaging contrast agent according to any of claims **1-8** and a carrier, adjuvant, or vehicle.	See above; VASOVIST is a pharmaceutical composition that comprises the diagnostic imaging contrast agent of Claim 2.
Claim 10. The pharmaceutical composition according to claim 9, further comprising a free organic ligand or a pharmaceutically acceptable salt thereof.	See above; VASOVIST is a pharmaceutical composition that includes the diagnostic imaging contrast agent of Claim 2 and includes the free organic ligand fosveset.

10. The relevant dates and information required pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) Investigational new drug (IND) application 51,172 for VASOVIST was initially submitted on July 19, 1996 and received by the Food and Drug Administration (FDA) on July 22, 1996. The IND effective date was 30 days thereafter on August 21, 1996.

(ii) New Drug Application (NDA) 21-171 was initially submitted on December 12, 2003 and was received by the FDA on December 15, 2003.

(iii) The NDA was approved on December 22, 2008.

11. Attached in **Appendix IV** is a brief description of the significant activities undertaken by Epix Pharmaceuticals, Inc. during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.

12. In the opinion of Epix Pharmaceuticals, Inc., U.S. Patent No. 6,676,929 is eligible for the extension herein applied for because it satisfies all of the requirements for such extension as follows:

35 U. S. C. § 156(a) and 37 C.F.R. § 1.720(a)

U.S. Patent No. 6,676,929 claims a product.

35 U. S. C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of U. S. Patent No. 6,676,929 has not expired before submission of this application.

35 U. S. C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of U.S. Patent No. 6,676,929 has never been extended.

35 U. S. C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

The application for extension is submitted by the owner of record.

35 U. S. C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

VASOVIST has been subject to a regulatory review period before its commercial marketing or use.

35 U. S. C. § 156(a)(5) and 37 C.F.R. § 1.720(e)

The commercial marketing of VASOVIST after the regulatory review period indicated herein is the first permitted commercial marketing of the product under the provisions of § 505 of the Food Drug & Cosmetic Act, under which such regulatory review occurred.

35 U.S.C. § 156(a)(5) and 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for VASOVIST.

(i) The length of the extension requested was determined by the following calculation:

(a) Effective date of IND: August 21, 1996.

(b) Effective date of NDA: December 15, 2003

(c) Date of issuance of U.S. Patent No. 6,676,929: January 13, 2004.

(d) Date of approval of NDA: December 22, 2008.

(ii) Span under 35 U. S. C. § 156 (g)(1)(B)(i) between August 21, 1996 and December 15, 2003 equals 2,673 days.

(iii) Span under 35 U. S. C. § 156 (g)(1)(B)(ii) between December 15, 2003 and December 22, 2008 equals 1,835 days.

(iv) The regulatory review period upon which the time for extension is calculated is the entire period set forth in (12)(ii) and (iii) above (4,508 days) less:

(a) The number of days in the regulatory review period prior to and including the date of patent issuance (January 13, 2004), i.e. 2,702 days; and

(b) The number of days during which the Applicant did not act with due diligence, i.e. zero days; and

(c) One half the number of days remaining in the period of (12)(ii) after subtracting the number of days prior to patent issuance in (12)(iv)(a) and the number of days the applicant did not act with due diligence in (12)(iv)(b), which is one half of 2,673 minus 2,702 or effectively 0 days.

(d) Accordingly, the length of patent extension is 4,508 minus the sum of 2,702 plus 0 plus 0, yielding 1,806 days.

The maximum extension allowable is 5 years, under 35 U. S. C. § 156(g)(6)(B)(i).

The period remaining in the term of U. S. Patent No. 6,676,929 from date of approval of NDA is 6 years, 5 months, and 5 days (i.e. 2,347 days) which, when added to the 1,806 days yields 4,153 days. 35 U.S.C. § 156(c) (3) provides that if the period remaining in the term of a patent after the date of the approval of the approved product when added to the regulatory review period exceeds fourteen years, the period of extension shall be reduced so that the total of both such periods does not exceed fourteen years. U.S. Patent No. 6,676,929 is to be extended a total of 1,806 days such that it will expire on May 5, 2020, which is less than fourteen years from date of NDA approval.

13. Epix Pharmaceuticals, Inc. acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought by this application.

14. The prescribed fee of $1,120.00 for receiving and acting upon the application for extension is enclosed. Please apply all other charges or credits to Deposit Account No. 06-1050.

15. All inquiries and correspondence relating to this application for patent term extension should be directed to:

Terry Mahn
Fish & Richardson P.C.
1425 K Street, N.W.
11th Floor
Washington, DC 20005
Telephone (202) 783-5070
Facsimile: (202) 783-2331

16. The application is accompanied by two additional copies of the application.

It is respectfully requested that the above Extension of the Patent term under 35 U. S. C. § 156 of the U. S. Patent No. 6,676,929 be granted.

Respectfully submitted,

Teresa Lavoie
Reg. No. 42,782

Fish & Richardson P.C.
60 South Sixth Street
3300 RBC Plaza
Minneapolis, MN 55402
Telephone: 612-335-5070
Facsimile: 612-288-9696

Enclosures: Appendices I, II, III, and IV

APPENDIX I

Certified Chain of Title

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 12, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON October 09, 2003.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498-005002
Client's Ref. No.: MET-4

RECORDATION FORM COVER SHEET
PATENTS ONLY

Commissioner for Patents: Please record the attached original document(s) or copy(ies).

1. Name of conveying party(ies):
Thomas J. McMurry, Hironao Sijiki, Daniel M. Scott and Randall B. Lauffer
Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):
MetaSyn, Inc.
71 Rogers Street
Cambridge, MA 02142-1118
Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment
☐ Merger
☐ Security Agreement
☐ Change of Name
☐ Other:
Execution Date: 12/21/95; 04/01/96; 12/21/95; 12/21/95; 12/21/95

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:
A. Patent Application No(s).:
10/034,522
B: Patent No(s).:
Additional numbers attached? ☐ Yes ☒ No

5. Name/address of party to whom correspondence concerning document should be mailed:
TERESA A. LAVOIE, PH.D.
Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 1

7. Total fee (37 CFR §3.41): $40
☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050
Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782
Name of Person Signing

Teresa A. Lavoie
Signature

10/9/03
Date

Total number of pages including coversheet, attachments and document: 17

60170885.doc

CH $40.00 061050 10034522

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

October 9, 2003
Date of Transmission

Angela J. Montgomery
Signature

Angela J. Montgomery
Typed Name of Person Signing Certificate

MET-4/CIP

PCT
ASSIGNMENT

We,

(1) Thomas J. McMurry,
(2) Hironao Sajiki,
(3) Daniel M. Scott, and
(4) Randall B. Lauffer,

residing, respectively, at

(1) 4 Bonad Road
Winchester, Massachusetts 01890 U.S.A.,
(2) 4-9 Fudo-cho
Gifu 500, Japan,
(3) 42 Nylander Way
Acton, Massachusetts 01720 U.S.A., and
(4) 23 Sumner Road, #2
Brookline, Massachusetts 02146 U.S.A.,

for good and valuable consideration, receipt of which is hereby acknowledged, have assigned, sold and transferred to, and do hereby assign, sell and transfer to MetaSyn, Inc., a corporation organized and existing under the laws of the Commonwealth of Massachusetts and having an office and a place of business at 71 Rogers Street, Cambridge, Massachusetts 02142-1118 U.S.A., its successors and assigns: (1) the entire right, title and interest in all countries throughout the world in and to any and all our inventions and discoveries disclosed in our International Patent Application, filed under the Patent Cooperation Treaty in the United States Receiving Office (RO/US), entitled: DIAGNOSTIC IMAGING CONTRAST AGENTS WITH EXTENDED BLOOD RETENTION, and designating Albania (AL), Armenia (AM), Australia (AU), Austria (AT), Azerbaijan (AZ), Barbados (BB), Belarus (BY), Belgium (BE), Benin (BJ),

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12/5/95

Brazil (BR), Bulgaria (BG), Burkina Faso (BF), Cameroon (CM), Canada (CA), Central African Republic (CF), Chad (TD), China (CN), Congo (CG), Cote d'Ivoire (CI), Czech Republic (CZ), Democratic People's Republic of Korea (KP), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Gabon (GA), Georgia (GE), Germany (DE), Greece (GR), Guinea (GN), Hungary (HU), Iceland (IS), Ireland (IE), Italy (IT), Japan (JP), Kazakhstan (KZ), Kenya (KE), Kyrgyzstan (KG), Latvia (LV), Lesotho (LS), Liberia (LR), Liechtenstein (LI), Lithuania (LT), Luxembourg (LU), Madagascar (MG), Malawi (MW), Mali (ML), Mauritania (MR), Mexico (MX), Monaco (MC), Mongolia (MN), Netherlands (NL), New Zealand (NZ), Niger (NE), Norway (NO), Poland (PL), Portugal (PT), Republic of Korea (KR), Republic of Moldova (MD), Romania (RO), Russian Federation (RU), Senegal (SN), Singapore (SG), Slovakia (SK), Slovenia (SI), Spain (ES), Sri Lanka (LK), Sudan (SD), Swaziland (SZ), Sweden (SE), Switzerland (CH), Tajikistan (TJ), the former Yugoslav Republic of Macedonia (MK), Togo (TG), Trinidad and Tobago (TT), Turkey (TU), Turkmenistan (TM), Uganda (UG), Ukraine (UA), United Kingdom (GB), United States of America (US), Uzbekistan (UZ) and Viet Nam (VN), [subsequently identified as International Patent Application No. PCT/US96/00164, filed 16 January 1996 *], including any renewals, revivals, reissues, re-examinations, extensions, continuations and divisions thereof, and any substitute applications therefor; (2) the full and complete right to file patent applications in the name of MetaSyn, Inc. its designee, or in our names at MetaSyn, Inc., or its designee's election,

---

* We hereby authorize MetaSyn, Inc. and its representatives to insert in this instrument the International Patent Application number and the filing date of said application when MetaSyn, Inc. is officially notified thereof.

ASSIGN.3
12/4/95

on the aforesaid inventions, discoveries and applications in all countries of the world; (3) the entire right, title and interest in and to any Letters Patent which may issue on the aforesaid inventions, discoveries and applications in any country of the world and any renewals, revivals, reissues, reexaminations and extensions thereof, and any patents of confirmation, registration and importation of the same; and (4) the entire right, title and interest in and to all Convention and Treaty Rights of all kinds thereon, including without limitation all rights of priority in any country of the world, in and to the following priority application(s):

08/382,317	United States	1 February 1995
application no.	country	filing date
application no.	country	filing date

and all rights of priority in any country of the world deriving from the above-identified International Patent Application.

We hereby authorize and request the competent authorities to grant and to issue any and all such Letters Patent in any country throughout the world to MetaSyn, Inc. as the assignee of the entire right, title and interest therein, as fully and entirely as the same would have been held and enjoyed by me/us had this assignment, sale and transfer not been made.

We agree, at any time, upon the request of MetaSyn, Inc. to execute and to deliver to MetaSyn, Inc. any additional applications for patents for said inventions and discoveries, or any part or parts thereof, and any applications for patents of confirmation, registration and importation based on any Letters Patent issuing on said inventions, discoveries or applications, and divisions,

continuations, renewals, revivals, reissues, reexaminations and extensions thereof.

We further agree, at any time, upon request of MetaSyn, Inc. to execute and to deliver to MetaSyn, Inc. such additional documents, if any, as are necessary or desirable to secure patent protection on said inventions, discoveries and applications throughout all countries of the world, and otherwise to do the necessary to give full effect to and to perfect any and all rights of MetaSyn, Inc. under this Assignment, including the execution, delivery and procurement of any and all further documents evidencing this assignment, transfer and sale as may be necessary or desirable.

ASSIGNORS:

X _____ (1)
Thomas J. McMurry

_____ (2)
Hironao Sajiki

X _____ (3)
Daniel M. Scott

X _____ (4)
Randall B. Lauffer

ASSIGN.3
12/4/95

On this 21st day of December, 1995, Thomas J. McMurry (1) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

On this _____ day of _____, _____, Hironao Sajiki (2) personally appeared before me, a Notary Public in and for _____, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

On this 21st day of December, 1995, Daniel M. Scott (3) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

ASSIGN.3
12/4/95

On this 21st day of December, 1995, Randall B. Lauffer (4) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

Notary Public

ACKNOWLEDGEMENT OF ASSIGNEE:

MetaSyn, Inc.

By: Randall B. Lauffer
Title: Chairman and Chief Scientific Officer

On this 21st day of December, 1995, Randall B. Lauffer personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and duly acknowledged the executed Assignment on behalf of the Assignee.

Notary Public

ASSIGN.3
12/4/95

Docket No. MET/4 CIP

NOTARIAL CERTIFICATE

I, Jennifer Elwell, a Notary Public in and for the State of New York, do hereby certify that I have compared the attached electrophotographic copy of an Assignment dated March 21, 1996, from Hironao Sajiki to MetaSyn, Inc., to the original of said Assignment and that the attached copy is a true copy of the original Assignment.

Jennifer Elwell

Signed at New York, New York
this 1st day of July, 1997

1999

MET-4/CIP

PCT
ASSIGNMENT

We,

(1) Thomas J. McMurry,
(2) Hironao Sajiki,
(3) Daniel M. Scott, and
(4) Randall B. Lauffer,

residing, respectively, at

(1) 4 Bonad Road
Winchester, Massachusetts 01890 U.S.A.,
(2) 4-9 Fudo-cho
Gifu 500, Japan,
(3) 42 Nylander Way
Acton, Massachusetts 01720 U.S.A., and
(4) 23 Sumner Road, #2
Brookline, Massachusetts 02146 U.S.A.,

for good and valuable consideration, receipt of which is hereby acknowledged, have assigned, sold and transferred to, and do hereby assign, sell and transfer to MetaSyn, Inc., a corporation organized and existing under the laws of the Commonwealth of Massachusetts and having an office and a place of business at 71 Rogers Street, Cambridge, Massachusetts 02142-1118 U.S.A., its successors and assigns: (1) the entire right, title and interest in all countries throughout the world in and to any and all our inventions and discoveries disclosed in our International Patent Application, filed under the Patent Cooperation Treaty in the United States Receiving Office (RO/US), entitled: DIAGNOSTIC IMAGING CONTRAST AGENTS WITH EXTENDED BLOOD RETENTION, and designating Albania (AL), Armenia (AM), Australia (AU), Austria (AT), Azerbaijan (AZ), Barbados (BB), Belarus (BY), Belgium (BE), Benin (BJ),

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3/4/96

Brazil (BR), Bulgaria (BG), Burkina Faso (BF), Cameroon (CM), Canada (CA), Central African Republic (CF), Chad (TD), China (CN), Congo (CG), Cote d'Ivoire (CI), Czech Republic (CZ), Democratic People's Republic of Korea (KP), Denmark (DK), Estonia (EE), Finland (FI), France (FR), Gabon (GA), Georgia (GE), Germany (DE), Greece (GR), Guinea (GN), Hungary (HU), Iceland (IS), Ireland (IE), Italy (IT), Japan (JP), Kazakhstan (KZ), Kenya (KE), Kyrgyzstan (KG), Latvia (LV), Lesotho (LS), Liberia (LR), Liechtenstein (LI), Lithuania (LT), Luxembourg (LU), Madagascar (MG), Malawi (MW), Mali (ML), Mauritania (MR), Mexico (MX), Monaco (MC), Mongolia (MN), Netherlands (NL), New Zealand (NZ), Niger (NE), Norway (NO), Poland (PL), Portugal (PT), Republic of Korea (KR), Republic of Moldova (MD), Romania (RO), Russian Federation (RU), Senegal (SN), Singapore (SG), Slovakia (SK), Slovenia (SI), Spain (ES), Sri Lanka (LK), Sudan (SD), Swaziland (SZ), Sweden (SE), Switzerland (CH), Tajikistan (TJ), the former Yugoslav Republic of Macedonia (MK), Togo (TG), Trinidad and Tobago (TT), Turkey (TU), Turkmenistan (TM), Uganda (UG), Ukraine (UA), United Kingdom (GB), United States of America (US), Uzbekistan (UZ) and Viet Nam (VN), [subsequently identified as International Patent Application No. PCT/US96/00164, filed 16 January 1996 *], including any renewals, revivals, reissues, re-examinations, extensions, continuations and divisions thereof, and any substitute applications therefor; (2) the full and complete right to file patent applications in the name of MetaSyn, Inc. its designee, or in our names at MetaSyn, Inc., or its designee's election,

---

* We hereby authorize MetaSyn, Inc. and its representatives to insert in this instrument the International Patent Application number and the filing date of said application when MetaSyn, Inc. is officially notified thereof.

ASSIGN.3
3/4/96

on the aforesaid inventions, discoveries and applications in all countries of the world; (3) the entire right, title and interest in and to any Letters Patent which may issue on the aforesaid inventions, discoveries and applications in any country of the world and any renewals, revivals, reissues, reexaminations and extensions thereof, and any patents of confirmation, registration and importation of the same; and (4) the entire right, title and interest in and to all Convention and Treaty Rights of all kinds thereon, including without limitation all rights of priority in any country of the world, in and to the following priority application(s):

08/382,317	United States	1 February 1995
application no.	country	filing date
application no.	country	filing date

and all rights of priority in any country of the world deriving from the above-identified International Patent Application.

We hereby authorize and request the competent authorities to grant and to issue any and all such Letters Patent in any country throughout the world to MetaSyn, Inc. as the assignee of the entire right, title and interest therein, as fully and entirely as the same would have been held and enjoyed by me/us had this assignment, sale and transfer not been made.

We agree, at any time, upon the request of MetaSyn, Inc. to execute and to deliver to MetaSyn, Inc. any additional applications for patents for said inventions and discoveries, or any part or parts thereof, and any applications for patents of confirmation, registration and importation based on any Letters Patent issuing on said inventions, discoveries or applications, and divisions,

continuations, renewals, revivals, reissues, reexaminations and extensions thereof.

We further agree, at any time, upon request of MetaSyn, Inc. to execute and to deliver to MetaSyn, Inc. such additional documents, if any, as are necessary or desirable to secure patent protection on said inventions, discoveries and applications throughout all countries of the world, and otherwise to do the necessary to give full effect to and to perfect any and all rights of MetaSyn, Inc. under this Assignment, including the execution, delivery and procurement of any and all further documents evidencing this assignment, transfer and sale as may be necessary or desirable.

ASSIGNORS:

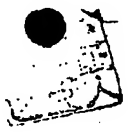
_____ (1)
Thomas J. McMurry

_____ (2)
Hironao Sajiki

_____ (3)
Daniel M. Scott

_____ (4)
Randall B. Lauffer

ASSIGN.3
3/4/96



On this _____ day of _____, _____, Thomas J. McMurry (1) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____
Notary Public

On this _____ day of _____, _____, Hironao Sajiki (2) personally appeared before me, a Notary Public in and for _____, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____
Notary Public

On this _____ day of _____, _____, Daniel M. Scott (3) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____
Notary Public

ASSIGN.3
3/4/96

On this _____ day of _____, _____, Randall B. Lauffer (4) personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and executed the foregoing Assignment and duly acknowledged to me that such Assignment was executed for the uses and purposes therein expressed.

_____
Notary Public

ACKNOWLEDGEMENT OF ASSIGNEE:

MetaSyn, Inc.

By: _____
Randall B. Lauffer
Title: Chairman and Chief Scientific Officer

On this 1st day of April, 1996, Randall B. Lauffer personally appeared before me, a Notary Public in and for the Commonwealth of Massachusetts, and duly acknowledged the executed Assignment on behalf of the Assignee.

_____
Notary Public

ASSIGN.3
3/4/96

登簿平成８年第 201 号

嘱託人 佐治木弘尚

は代理人 山本秀策 によつて当公証人の面前でこの証書の署名を自認した。

よつてこれを認証する。

平成 ８ 年 ３ 月 ２１ 日

当公証人役場において。

大阪市中央区平野町２丁目１番２号(沢の鶴ビル内)

大阪法務局所属

公証人 能登哲也 公証人之印

大阪法務局所属 公証人役場

Registered No. 201 -1996

NOTARIAL CERTIFICATE

This is to certify that SYUSAKU YAMAMOTO,
an agent of HIRONAO SAJIKI , has stated in
my very presence that said HIRONAO SAJIKI
acknowledged himself to have signed to the attached document.

Dated this 21st day of March, 1996

Tetsuya Noto

TETSUYA NOTO NOTARY
Osaka Legal Affairs Bureau
1 - 2, Hirano - Machi, 2 - Chome
Chuo - ku, Osaka Japan

OSAKA LEGAL AFFAIRS BUREAU
"NOTARY"
1-2 HIRANO-MACHI 2-CHOME,
CHUO-KU, OSAKA JAPAN

Docket No. MET/4 CIP

NOTARIAL CERTIFICATE

I, Jennifer Elwell, a Notary Public in and for the State of New York, do hereby certify that I have compared the attached electrophotographic copy of an Assignment dated December 21, 1995, from Thomas J. McMurry, Daniel M. Scott, and Randall B. Lauffer to MetaSyn, Inc., to the original of said Assignment and that the attached copy is a true copy of the original Assignment.

Jennifer Elwell

JENNIFER ELWELL
Notary Public, State of New York
Qualified in Richmond County
Certificate Filed in New York County
No. 43-4983279
Commission Expires June 24, 1999

Signed at New York, New York
this 1st day of July, 1997

WEEKLY STATUS OF SERVICES

The Public Records Division (PRD) processes and fills orders for both certified and uncertified copies of United States Patent and Trademark Office documents and records assignments and other documents related to title. This is an update of actual processing times for orders filled during the week of **Jan. 4-10, 2009:**

DOCUMENT SERVICES	Goal	Actual Processing Time
Certified Documents		
Patent Applications-As-Filed	**7 days**	**4 days**
Patent Related File Wrappers	**25 days**	**21 days**
Patent Copies	**10 days**	**2 days**
Patent Assignments	**10 days**	**4 days**
Trademark Applications-As-Filed	**7 days**	**3 days**
Trademark Related File Wrappers	**25 days**	**14 days**
Trademark Assignments	**10 days**	**3 days**
Trademark Registrations, Expedited	**5 days**	**2 days**
Trademark Registrations, Regular	**14 days**	**6 days**
Uncertified Documents		
Patent Copies	**5 days**	**1 day**
Plant Patents	**5 days**	**0 days**
Patent Assignments	**10 days**	**1 day**
Patent Related File Wrappers	**25 days**	**8 days**
Trademark Copies	**5 days**	**0 days**
Trademark Assignments	**10 days**	**1 day**
Trademark Related File Wrappers	**25 days**	**3 days**

Customers should use the above actual processing time for each product as a guide as to when they can expect their orders to be completed. In cases where an urgent deadline is approaching, contact Document Services Customer Service at (571) 272-3150 or 1(800) 972-6382 for assistance with a particular order.

Customers are encouraged to place orders through the Internet at
http://ebiz1.uspto.gov/oems25p

Orders may also be faxed to the Document Services Branch at (571) 273-3250. Information on the status of pending orders may be obtained by calling (571) 272-3150 or 1 (800) 972-6382 (outside the Washington, DC Metro area), or via E-mail to dsd@uspto.gov.

ASSIGNMENT SERVICES

Submission Method	Goal	Actual Processing Time
Internet (EFS, ePAS or eTAS)	2 days	1 day
Fax	10 days	1 day
Paper	14 days	1 day

The Assignment Services Branch is currently mailing recordation notices for paper documents received in the Public Records Division on January 7, 2009.

Customers should use the above actual processing times as a guide as to when they can expect their assignment submissions to be processed. **For fastest service customers are encouraged to file assignments via the Internet.**

Assignment submissions may be made via the Internet at **http://epas.uspto.gov/** for patent assignments and **http://etas.uspto.gov** for trademark assignments. Patent assignment submissions may also be made by selecting the "Electronic Filing (EFS)" option at **http://www.uspto.gov/ebc**.

Assignment submissions may also be faxed to the Assignment Services Branch at (571) 273-0140. Trademark assignment recordations may be reviewed online at **http://assignments.uspto.gov/assignments**. Information on the status of pending assignment recordations may be obtained by calling (571) 272-3350 or 1 (800) 972-6382 (outside the Washington, DC Metro area).

Marilyn Ricks-Beach for
01/13/09

Manager, Public Records Division

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 12, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON October 09, 2003.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498-005002
Client's Ref. No.: MET-4

RECORDATION FORM COVER SHEET
PATENTS ONLY

Commissioner for Patents: Please record the attached original document(s) or copy(ies).

1. Name of conveying party(ies):

MetaSyn, Inc.
71 Rogers Street
Cambridge, MA 02142-1118

Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Epix Medical, Inc.
71 Rogers Street
Cambridge, MA 02142-1118

Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment
☐ Merger
☐ Security Agreement
☒ Change of Name
☐ Other:

Execution Date: 11/13/1996

4. Application number(s) or patent number(s):

If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No(s).: 10/034,522

B: Patent No(s).:

Additional numbers attached? ☐ Yes ☒ No

5. Name/address of party to whom correspondence concerning document should be mailed:

TERESA A. LAVOIE, PH.D.
Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 1

7. Total fee (37 CFR §3.41): $40

☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050

Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782
Name of Person Signing

Teresa Lavoie
Signature

10/9/03
Date

Total number of pages including coversheet, attachments and document: 4

60170907.doc

CH $40.00 061050 10034522

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

October 9, 2003
Date of Transmission

Angela J. Montgomery
Signature

Angela J. Montgomery
Typed Name of Person Signing Certificate

State of Delaware

Office of the Secretary of State

I, EDWARD J. FREEL, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "METASYN, INC.", CHANGING ITS NAME FROM "METASYN, INC." TO "EPIX MEDICAL, INC.", FILED IN THIS OFFICE ON THE THIRTEENTH DAY OF NOVEMBER, A.D. 1996, AT 2 O'CLOCK P.M.

Edward J. Freel, Secretary of State

2179269 8100

971035030

AUTHENTICATION: 8321175

DATE: 02-07-97

STATE OF DELAWARE
SECRETARY OF STATE
DIVISION OF CORPORATIONS
FILED 02:00 PM 11/13/1996
960330666 – 2179269

CERTIFICATE OF AMENDMENT

OF

RESTATED CERTIFICATE OF INCORPORATION

METASYN, INC.

Metasyn, Inc., a corporation organized and existing under the laws of the State of Delaware (the "Corporation"), hereby certifies as follows, pursuant to Section 242 of the Delaware General Corporation Law:

FIRST: That the Board of Directors of the Corporation by unanimous written consent of its members, filed with the minutes of the Board of Directors, in accordance with the provisions of Section 141(f) and 242, respectively, of the General Corporation Law of the State of Delaware, duly adopted the following amendment to the Restated Certificate of Incorporation:

That Article FIRST of the Corporation's Restated Certificate of Incorporation be amended by deleting it in its entirety and replacing it with the following:

FIRST: The name of the Corporation is EPIX Medical, Inc.

SECOND: That the holders of a majority of the outstanding shares of the Corporations's Common Stock and Preferred Stock, voting together as a single class, voted in favor of said amendment by written consent.

THIRD: That said amendment was duly adopted in accordance with the provisions of Sections 228 and 242 of the General Corporation Law of the State of Delaware and written notice of this Certificate of Amendment has been given as provided by Section 228 of the General Corporation Law of the State of Delaware to every stockholder entitle to such notice.

IN WITNESS WHEREOF, Metasyn, Inc. has caused this Certificate of Amendment of its Restated Certificate of Incorporation to be signed by Michael D. Webb, President, and Randall B. Lauffer, its Secretary, on this 13th day of November, 1996.

METASYN, INC.

By: Michael D. Webb
Michael D. Webb, President

ATTEST:

By: Randall B. Lauffer
Randall B. Lauffer, Secretary

Docket No. MET/4 CIP

NOTARIAL CERTIFICATE

I, Jennifer Elwell, a Notary Public in and for the State of New York, do hereby certify that I have compared the attached electrophotographic copy of a certified copy of a Certificate of Amendment of Restated Certificate of Incorporation for MetaSyn, Inc., dated November 13, 1996, to the original of said document and that the attached copy is a true copy of the original document.

Jennifer Elwell

JENNIFER ELWELL
Notary Public, State of New York
Qualified in Richmond County
Certificate Filed in New York County
No. 43-4933279
Commission Expires June 24, 1999

Signed at New York, New York
this 1st day of July, 1997

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 09, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON December 05, 2003.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498-005002
Client's Ref. No.: MET-4

RECORDATION FORM COVER SHEET
PATENTS ONLY

Commissioner for Patents: Please record the attached original document(s) or copy(ies).

1. Name of conveying party(ies):

Thomas J. McMurry, Hironao Sijiki, Daniel M. Scott and Randall B. Lauffer

Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Epix Medical, Inc.
71 Rogers Street
Cambridge, MA 02142-1118

Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:

☒ Assignment
☐ Merger
☐ Security Agreement
☐ Change of Name
☐ Other:

Execution Date: 05/12/03; 11/29/03; 05/29/03; 05/12/03

4. Application number(s) or patent number(s):

If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No(s).:

10/034,522

B: Patent No(s).:

Additional numbers attached? ☐ Yes ☒ No

5. Name/address of party to whom correspondence concerning document should be mailed:

TERESA A. LAVOIE, PH.D.
Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 1

7. Total fee (37 CFR §3.41): $40

☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050

Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782
Name of Person Signing

Teresa A. Lavoie
Signature

12/5/03
Date

Total number of pages including coversheet, attachments and document: 6

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CH $40.00 061050 10034522

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

December 5, 2003
Date of Transmission

Angela J. Montgomery
Signature

Angela J. Montgomery
Typed Name of Person Signing Certificate

Attorney Docket No: 13498-005002/MET-4

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of May, 2003.

Thomas J McMurry L.S.

THOMAS J. MCMURRY

State of Massachusetts

: ss.

County of Middlesex:

Before me this 12th day of May, 2003, personally appeared **THOMAS J. MCMURRY** known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Barbara A. Murphy

Notary Public

My Commission Expires: Commission Expires 5/21/04

[Notary's Seal Here]

Attorney Docket No: 13498-005002/MET-4

IN TESTIMONY WHEREOF, I have hereunto set my hand this 29 day of November, 2003

Hironao Sijiki L.S.

HIRONAO SIJIKI

Attorney Docket No: 13498-005002/MET-4

IN WITNESS WHEREOF, I have hereunto set my hand this 29th day of May, 2003.

Daniel M. Scott L.S.
DANIEL M. SCOTT

State of Massachusetts :
: ss.
County of Middlesex :

Before me this 29th day of May, 2003, personally appeared **DANIEL M. SCOTT** known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Patricia A Hofstetter
Notary Public
My Commission Expires: May 19, 2006

[Notary's Seal Here]

Attorney Docket No: 13498-005002/MET-4

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of May, 2003.

RANDALL B. LAUFFER L.S.

State of Massachusetts :

: ss.

County of Middlesex :

Before me this 12th day of May, 2003, personally appeared **RANDALL B. LAUFFER** known to me to be the person whose name is subscribed to the foregoing Assignment and acknowledged that he executed the same as his free act and deed for the purposes therein contained.

Barbara A. Murphy
Notary Public

My Commission Expires:
Commission Expires 5/21/04

[Notary's Seal Here]

60122824.doc

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 12, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON June 18, 2003.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498-005002
Client's Ref. No.: MET-4

RECORDATION FORM COVER SHEET
PATENTS ONLY

Commissioner for Patents: Please record the attached original document(s) or copy(ies).

1. Name of conveying party(ies):

Epix Medical, Inc.
71 Rogers Street
Cambridge, MA 02142-1118

Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Schering Aktiengesellschaft
Muellerstrasse 170-178
13342 Berlin
GERMANY

Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment
☐ Merger
☒ Security Agreement
☐ Change of Name
☐ Other:

Execution Date: 05/26/2003

4. Application number(s) or patent number(s):

If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No(s).: 10/034,622

B: Patent No(s).:

Additional numbers attached? ☐ Yes ☒ No

5. Name/address of party to whom correspondence concerning document should be mailed:

MONICA MCCORMICK GRAHAM, PH.D.
Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 1

7. Total fee (37 CFR §3.41): $40

☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050

Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Monica McCormick Graham, Ph.D.
Reg. No. 42,600
Name of Person Signing

Signature

6/18/03
Date

Total number of pages including coversheet, attachments and document: 19

60146935.doc

CH $40.00 06/1050 10034522

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

June 18, 2003
Date of Transmission

Signature

Jill Hugo
Typed Name of Person Signing Certificate

~~EXHIBIT A~~ 9h

PATENT COLLATERAL ASSIGNMENT

This Agreement is made on the 21 day of May, 2003 between EPIX MEDICAL, INC. a Delaware corporation having a mailing address at 71 Rogers St., Cambridge, Massachusetts ("Assignor") and SCHERING AKTIENGESELLSCHAFT, a German corporation having a mailing address at 13342 Berlin, Germany ("Lender").

BACKGROUND

Assignor has executed and delivered its promissory note to the Lender pursuant to a certain Loan Agreement of even date herewith between Assignor and the Lender (as amended from time to time, the "Loan Agreement"). In order to induce the Lender to execute and deliver the Loan Agreement, Assignor has agreed to collaterally assign to Lender certain patent rights, all as more fully set forth in that certain Security Agreement of even date herewith between Assignor and Lender, a true copy of which is attached hereto as Exhibit A (the "Security Agreement").

NOW, THEREFORE, in consideration of the premises, Assignor hereby agrees with Lender as follows:

1. Capitalized terms not otherwise defined herein shall have the meanings ascribed to them in the Loan Agreement or the Security Agreement.

2. To secure the complete and timely satisfaction of all Obligations of Assignor to Lender, Assignor has granted, assigned and conveyed to Lender, pursuant to the terms and conditions of the Security Agreement, a security interest in Assignor's entire right, title and interest in and to, among other things, the Patents, Applications, Reissued Patents, Royalties, Claims and Proceeds thereof, including but not limited to those Patents and Applications listed in Schedule 1 attached to the Security Agreement that is attached hereto.

3. Assignor has agreed that, until all of the Obligations shall have been satisfied in full, it will not enter into any agreement (for example, a license agreement or patent assignment) which is inconsistent with Assignor's obligations and covenants under the Security Agreement.

4. Assignor authorizes Lender to modify this Agreement by amending Schedule 1 attached to the Security Agreement that is attached hereto to include any future Patents and Applications.

5. If any Event of Default shall have occurred and be continuing, Assignor hereby authorizes and empowers Lender to make, constitute and appoint any officer or agent of Lender, as Lender may select, in its exclusive discretion, as Assignor's true and lawful attorney-in-fact, with the power to endorse Assignor's name on all Applications, documents, papers and instruments necessary for Lender to use the Patents, or to grant or issue any exclusive or nonexclusive license under the Patents to any third person, or necessary for Lender to assign, pledge, convey or otherwise transfer title in or dispose of the Patents to any third person.

Assignor hereby ratifies all that such attorney shall lawfully do or cause to be done by virtue hereof. This power of attorney shall be irrevocable for the life of this Agreement.

WITNESS the execution hereof under seal as of the day and year first above written.

ATTEST:

ASSIGNOR:

EPIX MEDICAL, INC.

By Michael D. Webb

LENDER:

SCHERING AKTIENGESELLSCHAFT

By W. v. Heydebreck

By Lange

CERTIFICATE OF ACKNOWLEDGEMENT

COMMONWEALTH OR STATE OF Massachusetts
: ss
COUNTY OF Middlesex :

Before me, the undersigned, a Notary Public in and for the country aforesaid, on this 26 day of May, 2003, personally appeared Michael Webb to me known personally, and who, being by me duly sworn, deposes and says that he/she is the CEO of EPIX Medical, and that the seal affixed to the foregoing instrument is the corporate seal of said corporation, and that said instrument was signed and sealed on behalf of said corporation by authority of its Board of Directors, and said CEO acknowledged said instrument to be the free act and deed of said corporation.

Barbara J. Murphy
Notary Public
My commission expires:
Commission Expires 5/21/04

Final Version

SECURITY AGREEMENT

THIS SECURITY AGREEMENT (as amended, supplemented, restated or otherwise modified, the "Security Agreement") is entered into as of May 26, 2003, between EPIX MEDICAL, INC., a Delaware corporation, with its principal offices in Cambridge, Massachusetts (the "Debtor"), and SCHERING AKTIENGESELLSCHAFT, a German corporation having its principal offices at 13342 Berlin, Germany (the "Secured Party").

WHEREAS, on and as of the date hereof, the Debtor and Secured Party have executed and delivered a certain Loan Agreement providing for a maximum principal amount of loans of Dollars such Loan Agreement, and any and all amendments, modifications, extensions, restatements, renewals, refinancings and/or replacements thereof from time to time is hereinafter referred to as the "Loan Agreement"; and the Debtor has executed and delivered to Secured Party a certain Non-Negotiable Note ("Note") with a maximum principal amount of Dollars (such note, and any and all amendments, modifications, extensions, restatements, renewals, refinancings and/or replacements thereof from time to time being herein referred to as the "Note");

WHEREAS, the indebtedness evidenced by the Note is secured as hereinafter provided; and

WHEREAS, Debtor, in consideration of and in order to induce Secured Party, from time to time and in accordance with and subject to the provisions set forth in the Loan Agreement, to make advances aggregating to a maximum principal amount of Dollars has determined that it is in the best interest of Debtor to execute, deliver and perform this Security Agreement;

NOW, THEREFORE, for valuable consideration, the sufficiency and receipt of which are hereby acknowledged, the Debtor and the Secured Party hereby agree as follows:

1. Definitions. As used in this Security Agreement, and in addition to terms defined elsewhere in this Security Agreement, the following terms have the following meanings:

"Event of Default" shall mean (a) a breach or default by Debtor under this Security Agreement or (b) an Event of Default as defined in the Loan Agreement.

"Proceeds" has the meaning assigned to it under the Uniform Commercial Code, provided that Proceeds shall also be deemed to include (i) any and all proceeds of any insurance, indemnity, warranty or guaranty payable to Debtor from time to time with respect to any of the Secured Assets, and (ii) any and all payments (in any form whatsoever) made or due and payable to Debtor from time to time in connection with any requisition, confiscation, condemnation, seizure or forfeiture of all or any part of the Secured Assets by any Governmental Authority (or any Person acting under color of Governmental Authority), provided further that with respect to whatever is collected on, or distributed on account of Secured Assets, Proceeds shall mean exclusively any and all royalties from time to time paid or payable under or in connection with any of the Secured Assets after the date hereof.

"relating to" means "arising out of, in connection with or otherwise relating to", and "relates to" and "related to" each has a substantially similar meaning.

"Secured Assets" shall mean and include (i) all of the Debtor's right, title and interest in and to (a) any and all letters patent, or other patents, whether issued in the United States or any other country, and the inventions described and claimed therein relating to magnetic resonance imaging ("MRI"), including but not limited to those set forth on Schedule 1 attached hereto, whether in good standing or expired, whether now existing or hereinafter arising or created, and whether owned by Debtor singly or jointly with another Person (including but not limited to the "Joint Patents" as that term is defined in the Research Agreement (defined below)) or employed by Debtor pursuant to license or other grant (hereinafter referred to collectively as the "Patents"); (b) all applications for Patents and any Patent which may be issued upon any of said applications and any future patent applications of Debtor and all applications for re-instatement of any expired Patents (hereinafter referred to collectively as the "Applications"); (c) any reissue, extension, division or continuation of the Patents or the Applications (such reissues, extensions, divisions and continuations being herein referred to collectively as the "Reissued Patents"); (d) all future royalties or other fees paid or payment or payments made or to be made to the Debtor in respect of the Patents (the "Royalties"); and (ii) Proceeds of any and all of the foregoing (the Patents, Applications, Reissued Patents and Royalties and Proceeds being herein referred to collectively as the "Patent Rights"); (iii) all rights, interests, claims and demands that the Debtor has or may have in existing and future profits and damages for past and future infringements of the Patent Rights (such rights, interests, claims and demands being herein called the "Claims") (the Patent Rights and Claims collectively referred to as the "Patent Collateral"); (iv) all license and other agreements pursuant to which such Patent Rights were acquired; (v) all other intangible assets, including know-how, of every kind and description (including rights under any license agreement pursuant to which such know-how was granted), now owned or hereafter acquired by the Debtor, and whether now existing or hereafter arising, relating to any products involving MRI, and (vi) all books and records relating to the assets described in clauses (i), (ii), (iii), (iv) and (v), whether in writing or electronic form.

"Uniform Commercial Code" means the Uniform Commercial Code as the same may from time to time be in effect in the State of Delaware.

2. Definitions Incorporated. All capitalized terms used herein, unless otherwise specifically defined, shall have the meaning ascribed to such terms in the Loan Agreement, in the Note or in the Collaborative Research Agreement by and between the Debtor and the Secured Party, dated as of May 26, 2003, as thereafter amended, supplemented, restated or otherwise modified from time to time (the "Research Agreement"). It is agreed that in connection therewith, the Parties shall look first to the Loan Agreement, then to the Note and then to the Research Agreement. In the event of any conflict or inconsistency between the terms of the Loan Agreement, the Note, the Research Agreement and this Security Agreement, the Loan Agreement shall prevail.

3. Security Interest. The Debtor hereby grants to the Secured Party a security interest in all of the Debtor's right, title and interest in and to the Secured Assets to secure (i) the prompt and complete payment when due of all principal of and interest heretofore or hereafter owing or outstanding under the Loan Agreement and/or the Note, (ii) the prompt and complete payment when due by the Debtor of all costs and expenses (including reasonable attorney's fees

and expenses) incurred by the Secured Party in the collection of amounts due under and/or in enforcing its rights under the Loan Agreement, the Note and/or this Security Agreement and (iii) the prompt and complete performance when due by the Debtor of all its obligations under the Loan Agreement, the Note and/or this Security Agreement (the obligations listed in (i), (ii) and (iii) being referred to collectively herein as the "Obligations").

4. Debtor Remains Liable. Anything herein to the contrary notwithstanding, (i) Debtor shall remain liable under all contracts and agreements of every kind and nature whatsoever ("contracts and agreements" or "contracts or agreements") included in the Secured Assets to the extent set forth therein to perform all of its duties and obligations thereunder to the same extent as if this Security Agreement had not been executed, (ii) the exercise by the Secured Party of any of its rights hereunder shall not release Debtor from any of its duties or obligations under the contracts and agreements included in the Secured Assets, and (iii) unless the Secured Party in its exercise of any rights or remedies expressly assumes by written agreement any of the contracts or agreements, the Secured Party shall not have any obligation or other liability under the contracts and agreements included in the Secured Assets including without limitation to be obligated to perform any of the obligations or duties of Debtor thereunder or to take any action to collect or enforce any claim for payment assigned hereunder.

5. Records. Debtor will at all times keep accurate and complete records of all items included in the Secured Assets, and the Secured Party shall have the right at all reasonable times, following reasonable advance notice without material disruption to the business of the Debtor, to examine and inspect the same and to make copies thereof.

6. Representations, Warranties and Covenants of the Debtor. With respect to the Secured Assets, Debtor hereby represents, warrants and covenants to the Secured Party as follows:

(i) (A) Debtor is the sole owner of the Secured Assets, except for the assets listed in Schedule 6(i) attached hereto. No Subsidiary or Affiliate of Debtor owns or will own any Patent Rights rights under contracts or agreements or other rights or assets of any kind or nature relating to MRI.

(B) The Secured Assets listed in Schedule 6(i) hereof are licensed to Debtor and pursuant to the license agreements identified on that Schedule, true and complete copies of which license agreements have previously been provided to Lender. Debtor is in material compliance with all of each such license agreement, and each such license agreement is in full force and effect, enforceable in accordance with its terms, and has not been varied, amended or modified in any manner.

(ii) Until all principal and interest which may be outstanding under the Loan Agreement is indefeasibly paid in full, Debtor will have such rights of ownership or other rights to each item of the Secured Assets as Debtor has on and as of the date hereof, the same will be used solely in connection with the Debtor's business; all of the Secured Assets are free and clear of all Liens, including any security interests or collateral interests of any other party.

(iii) Debtor hereby authorizes Secured Party to file all financing statements and amendments and supplements thereto, if any, including continuation statements with respect to the Secured Assets reasonably necessary in the judgment of the Secured Party to perfect the

security interest in the Secured Assets granted hereby. At the written request of the Secured Party, Debtor will attend to the filing of any and all continuation statements, as may be reasonably requested by the Secured Party in order to continue the perfection of the security interests of the Secured Party hereunder.

(iv) Debtor shall, from time to time as requested by the Secured Party, take such action, including without limitation to execute and deliver to the Secured Party all such instruments, assignments, supplements, further assurances and security or other agreements, as may be reasonably required or reasonably requested by the Secured Party in order to perfect and continue the Secured Party's security interest in the Secured Assets hereunder and to provide the Secured Party with the full benefits contemplated by this Agreement.

(v) Debtor agrees to pay, and to hold the Secured Party harmless from, any and all Liabilities, costs and expenses (including, without limitation, reasonable legal fees and expenses) except those caused by the willful misconduct or gross negligence of the Secured Party (1) with respect to, or resulting from, any delay in paying, any and all withholding or other taxes which may be payable or determined to be payable with respect to any of the Secured Assets, and (2) in connection with any of the transactions contemplated by this Security Agreement.

(vi) Debtor will not create, incur or permit to exist, and it will defend the Secured Assets against, and it will take such other action as is necessary, or reasonably requested by the Secured Party, to promptly remove, any Lien or claim on or to the Secured Assets, other than the liens created hereby, and, subject to the terms of any agreements relating to licensed Secured Assets, it will defend the right, title and interest of the Secured Party in and to any of the Secured Assets against the claims and demands of all persons whomsoever.

(vii) Debtor will not sell or otherwise transfer in any manner whatsoever any of the Secured Assets, except upon the advance written consent of the Secured Party or as otherwise permitted under the Loan Agreement.

(viii) Debtor has the power to execute and deliver this Security Agreement and to perform its obligations hereunder and has taken all necessary action and has received all required consents (private and governmental) to authorize such execution, delivery and performance, and this Security Agreement constitutes the legal, valid and binding obligation of the Debtor, enforceable against it in accordance with its terms. Furthermore, the execution, delivery and performance of this Security Agreement by Debtor does not and will not violate any material Law applicable to Debtor in connection with the transactions contemplated hereby.

(ix) The execution, performance and delivery of this Security Agreement does not violate or conflict in any material respect with the terms or provisions of, or the Debtor's performance under, any contract or agreement by or to which the Debtor is a party, bound or subject.

(x) Debtor is not in material default under any contract or agreement by or to which the Debtor is now or hereafter a party, bound or subject that is part of the Secured Assets. Debtor will perform and comply in all material respects with all obligations under all provisions of any Document filed by Debtor with the Securities and Exchange Commission to which Debtor is a party or by which it or any of its assets is bound that relates to the Secured Assets, after giving effect to any applicable grace periods thereto.

(xi) Debtor does not transact and has not transacted within the past five (5) years, any part of its business under any trade names, division names, assumed names or other names.

(xii) Debtor is a Delaware corporation whose chief executive office is located at Cambridge, Massachusetts.

(xiii) (a) Debtor is the true and lawful exclusive owner of the Patent Rights set forth on Schedule 1 hereto; (b) the Patent Collateral is valid and enforceable; (c) Debtor has no notice of any suits or actions commenced or threatened against it, or notice of claims asserted or threatened against it, with reference to the Patent Rights and the interests granted herein; and (d) the Patent Rights and all interests granted herein are so granted free from all liens, charges, claims, options, licenses, pledges and encumbrances of every kind and character, except for licenses granted by Debtor set forth on Schedule 6(xiii) hereto.

(xiv) (a) until all of the Obligations have been satisfied in full, Debtor will not enter into any agreement, including without limitation, license agreements, which are inconsistent with Debtor's obligations under this Security Agreement; and (b) if Debtor acquires rights to any new Patent Collateral, the provisions of this Security Agreement shall automatically apply thereto and Debtor shall give the Lender prompt written notice thereof along with an amended Schedule 1.

Notwithstanding anything to the contrary contained herein, including, without limitation, the provisions of clauses (i), (v) and (vi) of this Section 6, Debtor may, prior to the occurrence of an Event of Default, without the consent of the Secured Party, grant licenses to or under the Secured Assets that are consistent with any existing or future license granted by the Debtor to the Secured Party or any of its affiliates, and any payments received by Debtor in connection with the grant of any such license (whether in the form of license fees, upfront payments, milestone payments, royalties or otherwise) shall not be considered Proceeds covered by the security interest granted to the Secured Party hereunder; provided that, all Proceeds from the grant of any such license that are received by the Debtor or which the Debtor is entitled to receive subsequent to the occurrence of an Event of Default shall be considered Proceeds covered by the security interest granted to the Secured Party hereunder.

7. Maintenance of Patent and Prosecution of Patent Application.

(a) Debtor shall, at its own expense, diligently maintain all Patents and diligently file and prosecute all Applications relating to the inventions described and claimed in the Patent Collateral in the United States Patent and Trademark Office, and shall pay or cause to be paid in their customary fashion all fees and disbursements in connection therewith, and shall not abandon any such Application prior to the exhaustion of all administrative and judicial remedies or disclaim or dedicate any Patent without the prior written consent of the Lender. Debtor shall not abandon any Patent Collateral without the prior written consent of the Lender, which shall not be unreasonably withheld.

(b) Any and all fees, costs and expenses, including reasonable attorneys' fees and expenses incurred by the Lender in connection with the preparation, modification, enforcement or termination of this Security Agreement and all other documents relating hereto and the consummation of this transaction; the filing and recording of any documents (including all taxes in connection therewith) in public offices, the payment or discharge of any taxes, counsel fees, maintenance fees, encumbrances or costs otherwise incurred in defending or prosecuting any

actions or proceedings arising out of or related to the Patent Collateral shall be paid by Debtor on demand by the Lender.

(c) Debtor shall have the right to bring suit in the name of Debtor to enforce the Patent Collateral, in which case the Lender may, at the Lender's sole option, be joined as a nominal party to such suit if the Lender shall be satisfied that such joinder is necessary and advisable and that the Lender is not thereby incurring any risk of liability by such joinder. Debtor shall promptly, upon demand, reimburse and indemnify, defend and hold harmless the Lender for all damages, costs and expenses, including reasonable attorneys' fees, incurred by the Lender pursuant to this paragraph and all other actions and conduct of Debtor with respect to the Patent Rights.

8. Secured Party's Duties. The powers conferred on the Secured Party hereunder are solely to protect its interest in the Secured Assets and shall not impose any duty of any kind or nature upon it to exercise any such powers. Secured Party shall have no obligation of any kind or nature to preserve rights against any Person.

9. Default Remedies.

(a) Except as expressly and unambiguously set forth herein, this Security Agreement shall be deemed absolute and without conditions. Upon an Event of Default, the Secured Party may enforce its rights with respect to the Secured Assets without first being required to attempt collection of any sums due from the Debtor. If an Event of Default shall occur, the Secured Party shall have the following rights:

(i) to perform any defaulted covenant or agreement of this Security Agreement, the Loan Agreement and the Research Agreement to such extent as the Secured Party shall reasonably determine and advance such monies as it shall deem reasonably advisable for the aforesaid purpose and all monies so advanced, together with interest thereon from the date advanced until paid at a rate per annum equal to the rate then in effect on the Note, shall be secured hereby and shall be repaid promptly after notice of the amount due without demand; provided, however, that nothing herein contained shall be construed to require the Secured Party to advance money for any of the aforesaid purposes;

(ii) to notify all account debtors, to the extent permitted by applicable Law, to pay directly to the Secured Party or otherwise as the Secured Party may specify all amounts it owes then or thereafter to Debtor until such time as the Secured Party has received all amounts to which it is entitled under the Note and this Security Agreement;

(iii) to take control of any and all proceeds to which the Secured Party may be entitled under this Security Agreement, the Loan Agreement, the Note, or under any applicable laws;

(iv) without demand of performance or other demand, advertisement or notice of any kind (except the notice specified below of time and place of public or private sale) to or upon Debtor or any other Person (all and each of which demands, advertisements and/or notices are hereby expressly waived), to take immediate possession of the Secured Assets, and, with or without taking possession of the Secured Assets, to sell, lease,

collect, receive, appropriate, realize upon or otherwise dispose of in any manner whatsoever (or contract to do so), any or all of the Secured Assets or any part thereof, at one or more times, either at public or private sale, upon commercially reasonable terms and in accordance with the UCC, and the Secured Party may become the purchaser thereof at any one or more public sale or sales and, to the extent permitted by Law, upon any one or more private sale or sales, free of any right or equity of redemption in Debtor, such right or equity being hereby released; provided that, any sale may be adjourned at any time and from time to time to a reasonably specified time and place by announcement at the time and place of sale or by publication or otherwise of the time and place of such adjourned sale; provided further that, the proceeds of any sale shall be applied (1) first to the expenses of taking, holding and preparing for sale or disposition, and sale or disposition and the like (including reasonable attorneys' fees), (2) next to the interest due under the Loan Agreement and/or the Note, (3) next to the principal due under Loan Agreement and/or the Note and the other amounts secured under clauses (i) and (ii) of Section 3 hereof, (4) next to all other amounts secured under Section 3 hereof, (5) next to the holder of any subordinate security interest therein if written notification of demand therefor is received and verified by the Debtor before distribution of the proceeds (or, if there is a dispute with respect thereto, the Secured Party can deposit such amount with a court or an appropriate third party) and (6) lastly, any surplus to Debtor and Debtor shall remain liable for any deficiency if the proceeds of any sales or other dispositions of the Secured Assets are insufficient to pay all amounts to which Secured Party is entitled, Debtor also being liable for the reasonable fees and expenses of any attorneys employed by Secured Party to collect such deficiency; and provided that, any such sale or sales, public or private, may be made on credit at the sole discretion of the Secured Party;

(v) to take immediate possession of the Secured Assets and to use or operate the Secured Assets in order to preserve the same or their value, and collect, receive and use all of the net profits from such use or operation to pay indebtedness secured by such Secured Assets; provided that, any continuing royalties or other similar amounts derived from the commercial sale of any products developed from the Secured Assets under the Research Agreement (as opposed to the sale of any products deriving from intellectual property that may be developed by the Secured Party) shall be allocated between the parties in accordance with Section 7.4.1 of the Research Agreement; provided further that, any sale or license by the Secured Party of any intellectual property included in the Secured Assets to any third party shall be deemed to be solely for the account of the Secured Party and not in any manner or portion for the account of Debtor or distributable to Debtor under and pursuant to the terms of the Research Agreement;

(vi) to require Debtor, to the extent practicable, to assemble the Secured Assets and make them available to the Secured Party at such locations as the Secured Party shall reasonably designate;

(vii) to enter all of the Debtor's facilities to remove the Secured Assets therefrom and take possession of the appropriate portions of the Debtor's books and records and computer hardware and software, and to use all of the same in a manner the Secured Party deems appropriate in order to preserve and sell or otherwise dispose of the Secured Assets;

(viii) to (without assuming any obligations or liability or any kind or nature thereunder), at any time and from time to time, enforce against any licensee or sublicensee all rights and remedies of the Debtor in, to and under any patent, know-how and/or other licenses included in the Secured Assets and, in the exercise of commercial reasonableness, take or refrain from taking any action under any such licenses, and the Debtor hereby releases the Secured Party free and harmless from and against any claims arising out of any lawful action so taken or omitted to be taken under applicable law with respect thereto;

(ix) to proceed to protect and enforce its rights under the Loan Agreement, the Note and this Security Agreement by a suit or suits in equity or at law, whether for specific performance or observance of any terms, provisions, covenants or conditions herein or therein contained in aid of the execution of any power therein or herein granted, for any foreclosure hereunder or thereunder, or for the enforcement of any other proper legal or equitable remedy;

(x) to exercise any such additional and/or different rights or remedies as are provided for in the Loan Agreement and/or the Note; and

(xi) to act as true and lawful attorney-in-fact of the Debtor, with full power of substitution, with full irrevocable power and authority in the place and stead of the Debtor, in the name of the Debtor, or in its own name, for the purpose of carrying out the terms of this Security Agreement, to take any and all appropriate action, including, without limitation, to execute, deliver, record and file any and all Documents which may be reasonably necessary or desirable to accomplish the purposes of this Security Agreement.

(b) The Secured Party shall, in addition, have any and all other rights and remedies provided by law or equity, including, without limitation, the rights and remedies of a secured party under the Uniform Commercial Code. All of the Secured Party's rights and remedies will be cumulative, and no waiver of any default will affect any other subsequent default. The rights and remedies provided in this Security Agreement are cumulative, may be exercised concurrently or separately, may be exercised from time to time and in such order, without any marshalling, as the Secured Party shall determine. Debtor expressly acknowledges that the Secured Party is not obligated to first foreclose its security interest in the Joint Patents, the decision as to the order in which the Secured Assets are to be addressed hereunder being in Lender's sole and absolute discretion. To the extent permitted by applicable Law, Debtor waives all claims, damages and demands against Secured Party arising out of the repossession, retention, sale or other disposition of the Secured Assets. Nothing herein contained shall be construed as preventing the Secured Party from taking all reasonable and lawful actions to protect its interest in the event that liquidation, insolvency, bankruptcy, reorganization or foreclosure proceedings of any nature whatsoever affecting the property or assets of Debtor are voluntarily or involuntarily instituted. The Secured Party's sole duty with respect to the Secured Assets, including, without limitation the custody, safekeeping and physical preservation of the Secured Assets shall be those duties which are imposed by the Uniform Commercial Code and cannot, by contract, be waived or otherwise eliminated. Neither the Secured Party, nor any of its respective directors, officers, employees or agents shall be liable for failure to demand, collect or realize upon all or any part of the Secured Assets or for any delay in doing so or shall be under any

obligation to sell or otherwise dispose of any Secured Assets upon the request of the Debtor or otherwise.

(c) (i) The Debtor expressly acknowledges that the Secured Party may record evidence of this Security Agreement and the security interest created hereby with the appropriate government filing/recording office(s) in such countries as the Secured Party desires in its sole discretion, whether by filing or recording a Patent Collateral Assignment in the form of Exhibit A attached hereto or with such other forms as may be customary, necessary and appropriate for similar use in a particular country. The Debtor agrees to execute and deliver promptly all such forms presented to it by the Secured Party.

(ii) Contemporaneously herewith, the Debtor shall execute and deliver to the Secured Party a Patent Assignment in the form attached hereto as Exhibit B (and such other forms as may be customary, necessary and appropriate for similar use in a particular country other than the United States of America that the Secured Party may present to the Debtor in the future) permanently assigning all Debtor's rights in the Patent Collateral to the Secured Party. Such assignment document(s) shall be held by the Secured Party in escrow until the occurrence of an Event of Default hereunder or under the Loan Documents. After such occurrence, in addition to all other rights and remedies of the Secured Party set forth herein, the Secured Party may, at its sole option, record such escrowed documents with the United States Patent and Trademark Office and with the appropriate government filing/recording office(s) in such other countries as the Secured Party desires in its sole discretion.

10. General Provisions.

(a) This Security Agreement and the security interests of the Secured Party in the Secured Assets created hereby shall cease and terminate only upon final indefeasible repayment in full of the principal and any accrued interest under and pursuant to the Loan Agreement.

(b) Debtor hereby waives all demands, notices, presentments, claims, defenses and protests of any kind, except (if any) as expressly and unambiguously provided herein and unless not permitted by applicable law.

(c) This Security Agreement shall be construed to be a contract made under and pursuant to the laws of the State of New York, and all of the terms, covenants and conditions contained herein shall be governed by and construed in accordance with such laws, without giving effect to the conflict of laws principles contained in such laws.

(d) This Security Agreement, all supplements hereto and all amendments hereof, shall inure to the benefit of and be binding upon the Debtor, the Secured Party, and their respective successors and assigns; but this Security Agreement may not be assigned by Debtor or the Secured Party without the advance written consent of the other party; provided, however, that the Secured Party may assign this Security Agreement to an Affiliate without the Debtor's advance consent.

(e) No course of dealing between the Debtor and the Secured Party or any delay on the part of the Secured Party in exercising any rights hereunder shall affect the rights of the Secured Party, on any future occasion, to insist on strict compliance with the terms hereof or to exercise any available remedy. All consents and waivers shall be in writing. No waiver by

either party of any term, provision, covenant or condition contained in this Security Agreement, or of any breach of any such term, provision, covenant or condition, shall constitute a waiver by that party of any subsequent breach or justify or authorize the non-observance by the other party on any other occasion of such term, provision, covenant or condition contained in this Security Agreement.

(f) Subject to the provisions of Section 7.4 of the Loan Agreement, the invalidity or unenforceability of any term or condition hereof shall not affect the validity or enforceability of any other term or condition hereof or of this Security Agreement as a whole and each such term or condition which is enforceable in part but not enforceable in whole shall be enforced to the maximum extent permitted by applicable law.

(g) Titles of Sections and Subsections are for convenience only, and shall not modify rights and obligations created hereby. All references herein to Sections or Subsections shall refer to the corresponding Sections or Subsections of this Security Agreement unless specific reference is made to Sections or Subsections of another document. Use of the words "hereby", "herein", "hereto", "hereof", "hereunder" and similar words shall be deemed to refer to this Security Agreement in its entirety and not merely to the Sections or Subsections wherein any such word may appear unless otherwise specifically herein provided to the contrary. No one Party shall be deemed or construed as the drafter of this Security Agreement, and this Security Agreement shall not be construed more severely against any Party.

(h) All of the terms, covenants and conditions contained in this Security Agreement shall be binding upon and inure to the benefit of the parties hereto and their respective successors and assigns, provided that Debtor's obligations hereunder may not be delegated to any other person without the prior consent of Secured Party and any such attempted delegation without such consent shall be void.

(i) DEBTOR HEREBY WAIVES ANY RIGHT TO TRIAL BY JURY.

(j) No remedy herein conferred upon the Secured Party is intended to be exclusive of any other remedy and each and every such remedy shall be cumulative and shall be in addition to every other remedy provided hereunder or now or hereafter existing at law or in equity.

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IN WITNESS WHEREOF, the parties have caused this Security Agreement to be executed at the time first above written by their officers thereunto duly authorized.

SCHERING AKTIENGESELLSCHAFT
("SECURED PARTY")

Name: Prof. Dr. Günter Stock
Title: Member of the Vorstand

Name: Prof. Dr. Björn Wallmark
Title: Head of Corporate Research

EPIX MEDICAL, INC.
("DEBTOR")

Name: Michael D. Webb
Title: CEO

Schedule 1	Certain Patents and Patent Applications
Schedule 6(i)	Secured Assets that are licensed to Debtor
Schedule 6(xiii)	License in the Secured Assets granted by Debtor
Exhibit A	Form of Patent Collateral Assignment
Exhibit B	Form of U.S. Patent Assignment

STATE OF Massachusetts)
) SS:
COUNTY OF Middlesex)

BE IT REMEMBERED, that on this 23 day of May, 2003, before me the subscriber, a Notary Public of the State of Massachusetts personally appeared, Richard Webb, the CEO of IPIX MEDICAL, INC., a Delaware corporation, who, I am satisfied, is the person who executed the within instrument as the CEO of said company, and he acknowledged that he signed, sealed with the proper corporate seal and delivered the same as such officer, that the within instrument is the voluntary act and deed of said company made by virtue of authority of its board of directors, and that he received a true copy of the within instrument on behalf of said company.

Barbara A Murphy
Notary Public to the Commonwealth of Massachusetts
[Seal]

Commission Expires: 5/21/04

Schedule 1
Secured Assets

The following patent families constitute existing utility applications assigned to EPIX or in the case of the MET-1 patent family exclusively licensed from The General Hospital Corporation of Boston, Massachusetts (Agreement of March 24, 1992 amended July 10, 1995). MET-9 is assigned to Dyax and EPIX with EPIX having exclusive rights to MRI applications (Agreement of June 20, 1997 amended March 17, 2003).

MET-1	US	4,899,755
	US-CIP	4,880,008
	PCT	WO 86/06605
	EPO	222,886
	CANADA	1,264,663
	HONG KONG	1,000,311
	LATVIA	11,981
	SINGAPORE	43,886
MET-3	US	5,582,814
	PCT	WO 95/28179
MET-4	PCT	WO 96/23526
	AUSTRALIA	689,700
	ISRAEL	382,317
	NEW ZEALAND	301,181
	SINGAPORE	44,280
	SOUTH AFRICA	96/0417
	SWAZILAND	RP/17/99
	TAIWAN	90,445
MET-5	US CON Publication	US 2002/0034476
	PCT	WO 97/36619
	EPO	TO ISSUE
	AUSTRALIA	726,914
	CHINA	TO ISSUE
	ISRAEL	125,895
	NEW ZEALAND	331,629
	SINGAPORE	56,316
MET-6	US	5,919,967
	PCT	WO 98/46612
	AUSTRALIA	728,902
	NEW ZEALAND	337,921
MET-7	AUSTRALIA	742,438
	EPO	TO ISSUE
	NEW ZEALAND	503,402

MET-8	US PCT	TO ISSUE WO 01/08712
MET-9	US Application PCT	09/627,806 WO 01/09188
MET-10	US PCT	6,548,044 WO 01/37630
MET-11	PCT	WO 01/52906
MET-12	US PCT	6,549,798 WO 0262220
MET-14	PCT	WO 03/011115
MET-15	PCT	WO .03/13573
MET-16	US Publication PCT	US 2003/002810 WO 02/01113

Schedule 6(i)
Collateral not Owned

EPIX' MET-1 family of world patents listed below is exclusively licensed from The General Hospital Corporation of Boston, Massachusetts (Agreement of March 24, 1992 amended July 10, 1995). There are EPO divisional and Japanese applications being prosecuted by EPIX.

MET-1 Patents	
US	4,899,755
US-CIP	4,880,008
PCT	WO 86/06605
EPO	222,886
CANADA	1,264,663
HONG KONG	1,000,311
LATVIA	11,981
SINGAPORE	43,886

Schedule 6 (xiii)

Licenses Granted by Debtor

Strategic Collaboration Agreement dated June 9, 2000 with Schering AG

Amendment No. 1 to Strategic Collaboration Agreement dated December 22, 2000 with Schering AG

Worldwide License Agreement dated September 25, 2001 with Bracco Imaging SPA

Amended and Restated Strategic Collaboration Agreement dated June 9, 2000 with Tyco/Mallinckrodt Inc

Development and License Agreement dated March 29, 1996, as amended October October 4, 1999 with Daiichi Radioisotope Laboratories, Ltd

Reacquisition Agreement dated December 22, 2000 with Daiichi Radioisotope Laboratories, Ltd

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 12, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON March 29, 2005.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498-001001

RECORDATION FORM COVER SHEET
PATENTS ONLY

Commissioner for Patents: Please record the attached original document(s) or copy(ies).

1. Name of conveying party(ies):
EPIX MEDICAL, INC.
Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):
EPIX Pharmaceuticals, Inc.
161 First Street
Cambridge, MA 02142
Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:
☐ Assignment
☐ Merger
☐ Security Agreement
☒ Change of Name
☐ Other:
Execution Date: 09/07/2004

4. Application number(s) or patent number(s):
If this document is being filed with a new application, the execution date of the application is:
A. Patent Application No(s).: **See Attached Addendum**
B: Patent No(s).: **See Attached Addendum**
Additional numbers attached? ☒ Yes ☐ No

5. Name/address of party to whom correspondence concerning document should be mailed:
TERESA A. LAVOIE, PH.D.
Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 1

7. Total fee (37 CFR §3.41): **$2520.00**
☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050
Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

DO NOT USE THIS SPACE

9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782
Name of Person Signing

Teresa A. Lavoie
Signature

3/29/05
Date

Total number of pages including coversheet, attachments and document: 9

CH $2520.00 061050 60014448

60284533.doc

CERTIFICATE OF TRANSMISSION BY FACSIMILE

I hereby certify that this correspondence is being transmitted by facsimile to the Patent and Trademark Office on the date indicated below.

March 29, 2005
Date of Transmission

Angela J. Montgomery
Signature

Angela J. Montgomery
Typed Name of Person Signing Certificate

RECORDATION FORM COVER SHEET
PATENTS ONLY
(ADDENDUM)

Additional Patent Nos.

5,919,967	6,652,835	6,861,045
6,548,044	6,676,929	
6,549,798	6,709,646	

Additional Patent Application Nos.

60/014,448	60/486,833	10/487,025
60/146,414	60/495,178	10/492,108
60/163,650	60/503,221	10/635,838
60/167,257	60/543,875	10/755,506
60/177,580	60/606,988	10/755,507
60/308,690	60/649,713	10/758,729
60/308,721	08/382,317	10/786,791
60/311,557	08/460,921	10/850,134
60/330,156	08/463,121	10/888,833
60/381,524	08/463,290	10/961,872
60/381,652	08/463,941	
60/395,146	08/469,013	
60/401,617	08/823,643	
60/402,195	08/875,365	
60/466,237	08/942,989	
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60/466,396	10/291,900	
60/466,397	10/354,723	
60/466,452	10/365,350	
60/473,369	10/445,544	

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF AMENDMENT OF "EPIX MEDICAL, INC.", CHANGING ITS NAME FROM "EPIX MEDICAL, INC." TO "EPIX PHARMACEUTICALS, INC.", FILED IN THIS OFFICE ON THE SEVENTH DAY OF SEPTEMBER, A.D. 2004, AT 2:37 O'CLOCK P.M.

A FILED COPY OF THIS CERTIFICATE HAS BEEN FORWARDED TO THE NEW CASTLE COUNTY RECORDER OF DEEDS.

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

2179269 8100

040647513

AUTHENTICATION: 3335621

DATE: 09-07-04

State of Delaware
Secretary of State
Division of Corporations
Delivered 02:37 PM 09/07/2004
FILED 02:37 PM 09/07/2004
SRV 040647513 - 2179269 FILE

CERTIFICATE OF AMENDMENT

OF

RESTATED CERTIFICATE OF INCORPORATION

OF

EPIX MEDICAL, INC.

It is hereby certified that:

1. The name of the corporation (hereinafter called the "Corporation") is EPIX MEDICAL, INC.

2. The Certificate of Incorporation of the Corporation was filed on November 28, 1988 under the name Metacorp, Inc. A Certificate of Amendment to Certificate of Incorporation was filed on May 4, 1989 to change the name of the Corporation to Metasyn, Inc. A Certificate of Amendment to the Restated Certificate of Incorporation filed on May 29, 1996 was filed on November 13, 1996 to change the name of the Corporation to EPIX Medical, Inc. Thereafter a Restated Certificate of Incorporation ("Restated Certificate") was filed on February 4, 1997. A Certificate of Amendment to the Restated Certificate was filed on May 3, 2000. The said Restated Certificate as amended is hereby further amended to change the name of the Corporation by striking out Article FIRST thereof and by substituting in lieu of said Article the following new Article:

"FIRST: The name of the Corporation is EPIX Pharmaceuticals, Inc."

3. The amendment of the restated certificate of incorporation herein certified has been duly adopted in accordance with the provisions of Section 242 of the General Corporation Law of the State of Delaware.

IN WITNESS WHEREOF, the Corporation has caused this certificate to be signed by its Senior Vice President, Finance and Administration and Chief Financial Officer on the 7th day of September, 2004.

Peyton J. Marshall
Senior Vice President, Finance and
Administration and Chief Financial Officer

TRA 1904704v1

ATTACHMENT A

F&R Matter No.	Status	Serial No.	Filing Date	Patent Number	Issue Date	Title
13498-009003	PENDING	10/961,872	10/8/2004			CONTRAST-ENHANCED DIAGNOSTIC IMAGING METHOD FOR MONITORING INTERVENTIONAL THERAPIES
13498-013P01	EXPIRED	60/146,414	7/29/1999			TARGETING MULTIMERIC IMAGING AGENTS
13498-013001	ISSUED	09/627,719	7/28/2000	6,652,835	11/25/2003	TARGETING MULTIMERIC IMAGING AGENTS THROUGH MULTILOCUS BINDING
13498-013002	PUBLISHED	10/445,544	5/27/2003			TARGETING MULTIMERIC IMAGING AGENTS THROUGH MULTILOCUS BINDING
13498-013P02	EXPIRED	60/163,650	11/4/1999			TARGETING MULTIMERIC IMAGING AGENTS THROUGH MULTIVALENT BINDING
13498-010P01	EXPIRED	60/308,721	7/30/2001			PEPTIDE-BASED MULTIMERIC TARGETED CONTRAST AGENTS
13498-010001	ALLOWED	10/209,172	7/30/2002			PEPTIDE-BASED MULTIMERIC TARGETED CONTRAST AGENTS
13498-010002	PUBLISHED	10/209,183	7/30/2002			PEPTIDE-BASED MULTIMERIC TARGETED CONTRAST AGENTS
13498-010003	PENDING	10/786,791	2/25/2004			PEPTIDE-BASED MULTIMERIC TARGETED CONTRAST AGENTS
13498-011P01	EXPIRED	60/311,557	8/10/2001			PROTEINS CONJUGATES WITH EXTENDED CIRCULATING HALF-LIVES
13498-011001	CLOSED					PROTEINS CONJUGATES WITH EXTENDED CIRCULATING HALF-LIVES
13498-011US1	PUBLISHED	10/487,025	2/17/2004			POLYPEPTIDE CONJUGATES WITH EXTENDED CIRCULATING HALF-LIVES
13498-012P01	EXPIRED	60/308,690	7/30/2001			SYSTEMS AND METHODS FOR TARGETED MAGNETIC RESONANCE IMAGING OF THE VASCULATURE
13498-012001	PUBLISHED	10/209,416	7/30/2002			SYSTEMS AND METHODS FOR TARGETED MAGNETIC RESONANCE IMAGING OF THE VASCULAR SYSTEM
13498-014P01	CLOSED					NEOGENESIS HUMAN SERUM ALBUMIN LIGANDS
13498-015P01	ABANDONED	60/381,652	5/17/2002			AGENTS AND METHODS FOR VULNERABLE PLAQUE IMAGING
13498-016P01	ABANDONED	60/381,524	5/17/2002			AGENTS AND METHODS FOR MYOCARDIAL PERFUSION IMAGING
13498-017P01	ABANDONED	60/395,146	7/9/2002			TARGETED REACTIVE OXYGEN SCAVENGERS

F&R Matter No.	Status	Serial No.	Filing Date	Patent Number	Issue Date	Title
13498-018P01	ABANDONED	60/402,195	8/9/2002			FIBRIN TARGETED THERAPEUTICS
13498-019P01	EXPIRED	60/014,448	4/1/1996			BIOACTIVATED DIAGNOSTIC IMAGING CONTRAST AGENTS
13498-019001	ABANDONED	08/823,643	3/25/1997			BIOACTIVATED DIAGNOSTIC IMAGING CONTRAST AGENTS
13498-019002	ISSUED	09/952,971	9/14/2001	6,709,646	3/23/2004	BIOACTIVATED DIAGNOSTIC IMAGING CONTRAST AGENTS
13498-019003	PUBLISHED	10/758,729	1/16/2004			BIOACTIVATED DIAGNOSTIC IMAGING CONTRAST AGENTS
13498-020P01	EXPIRED	60/401,617	8/6/2002			PEPTIDE AGGREGATES
13498-020001	PUBLISHED	10/635,838	8/6/2003			PEPTIDE AGGREGATES
13498-003001	ABANDONED	08/382,317	2/1/1995			DIAGNOSTIC IMAGING CONTRAST AGENTS WITH EXTENDED BLOOD RETENTION
13498-023P01	EXPIRED	60/167,257	11/22/1999			IMAGING SEXUAL RESPONSE (MET-10)-PROVISIONAL
13498-023001	ISSUED	09/718,161	11/21/2000	6,548,044	4/15/2003	IMAGING SEXUAL RESPONSE
13498-023002	PUBLISHED	10/291,900	11/8/2002			IMAGING SEXUAL RESPONSE
13498-024P01	EXPIRED	60/177,580	1/22/2000			MAGNETIC RESONANCE IMAGING USING CONTRAST AGENTS BIOACTIVATED BY ENZYMATIC CLEAVAGE
13498-024001	PUBLISHED	10/200,477	7/19/2002			MAGNETIC RESONANCE IMAGING USING CONTRAST AGENTS BIOACTIVATED BY ENZYMATIC CLEAVAGE
13498-029P01	ABANDONED	60/466,396	4/28/2003			SELF-ASSEMBLED REACTIVE OXYGEN SCAVENGERS
13498-028P01	ABANDONED	60/466,239	4/28/2003			SELF-AGGREGATING MRI CONTRAST AGENTS
13498-027P01	ABANDONED	60/466,238	4/28/2003			CHELATING LIGANDS
13498-025P01	ABANDONED	60/466,237	4/28/2003			MACROPHAGE TARGETED CONTRAST AGENTS
13498-026P01	ABANDONED	60/466,395	4/28/2003			HIGH SENSITIVITY MRI CONTRAST AGENTS
13498-031P01	ABANDONED	60/466,397	4/28/2003			AGENTS AND METHODS FOR IMAGING INTRAVASCULAR LESIONS
13498-030P01	ABANDONED	60/466,452	4/28/2003			AGENTS AND METHODS FOR MYOCARDIAL IMAGING
13498-032P01	ABANDONED	60/466,393	4/28/2003			HYDROXAMIC ACID CHELATING LIGANDS
13498-033P01	EXPIRED	60/473,369	5/23/2003			OPTICALLY PURE AND ENRICHED ISOMERS OF CHELATING LIGANDS AND CONTRAST AGENTS

A 7164697

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 12, 2009

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF A DOCUMENT RECORDED ON November 14, 2006.

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

P. SWAIN
Certifying Officer

Substitute Form PTO-1595
Attorney Docket No.: 13498
Client's Ref. No.: MET-4

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1. Name of conveying party(ies):

SCHERING AKTIENGESELLSCHAFT
MUELLERSTRASSE 170-178
13342 BERLIN, GERMANY

Additional name(s) attached? ☐ Yes ☒ No

2. Name and address of receiving party(ies):

Epix Pharmaceuticals, Inc.
4 Maguire Road
Lexington, MA 02421

Additional names/addresses attached? ☐ Yes ☒ No

3. Nature of conveyance:

☐ Assignment
☐ Merger
☐ Security Agreement
☐ Change of Name
☒ Other: Termination of Security Agreement

Execution Date: 01/04/2006

4. Application number(s) or patent number(s):

If this document is being filed with a new application, the execution date of the application is:

A. Patent Application No(s).:

10/445,544

B: Patent No(s).:

7,011,815; 5,919,967; 6,549,798; 6,676,929; 6,861,045; 6,652,835; 6,709,646; 6,548,044; 6,969,507

Additional numbers attached? ☐ Yes ☒ No

5. Name/address of party to whom correspondence concerning document should be mailed:

TERESA A. LAVOIE, PH.D.
Fish & Richardson P.C.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402

6. Total number of applications/patents involved: 10

7. Total fee (37 CFR §3.41): $400

☐ Enclosed
☒ Authorized to charge Deposit Account.

8. Deposit Account No.: 06-1050

Please apply any additional charges, or any credits, to our Deposit Account No. 06-1050.

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9. Statement and Signature: *To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.*

Teresa A. Lavoie, Ph.D.
Reg. No. 42,782
Name of Person Signing

Teresa A Lavoie
Signature

11/14/06
Date

Total number of pages including coversheet, attachments and document: pages

60387735.doc

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11/14/2006 — Meredith Mescher — MEREDITH MESCHER
Date of Transmission — Signature — Typed Name of Person Signing Certificate

SCHERING

By fax and courier
Epix Pharmaceuticals, Inc.
Chief Executive Officer
Michael J. Astrue
161 First Street
Cambridge, MA 02142
USA

Schering AG

E: jurgen.schmitz-doerner@schering.de
T: +49.30.468- 15512
+49.30.468- 11 11
F: +49.30.468- 11411

Your Ref.	Your letter dated	Our Ref. (please indicate when replying)	Date
		RA/Sd/ZI (5b0412_1)	2006-01-04

Loan Agreement of May 26, 2003;
your notice of termination

Dear Sir,

We hereby acknowledge receipt of Epix' termination notice for the above mentioned Loan Agreement on January 4, 2006. We confirm that as of today Epix has repaid to Schering all Obligations (as defined in the Loan Agreement). Return of the original Note marked "cancelled" and confirmation of the filing of the UCC termination statement each will be sent under separate cover.

Yours sincerely,

Schering Aktiengesellschaft

Dr. Schmitz-Dörner

Dr. Schmitz-Dörner

PROMISSORY NOTE

Maximum Principal Balance of US$15,000,000.00

Date: May 26, 2005
Cambridge, Massachusetts

This Promissory Note ("Note") is executed and delivered under and pursuant to the terms of that certain Loan Agreement dated as of the date hereof (as amended, restated, supplemented or modified from time to time, the "Loan Agreement") by and between EPIX MEDICAL, INC., a Delaware corporation with a place of business at 71 Rogers Street, Cambridge, Massachusetts ("Borrower"), and SCHERING AKTIENGESELLSCHAFT, a German corporation ("Lender"). Capitalized terms not otherwise defined herein shall have the meanings provided in the Loan Agreement.

FOR VALUE RECEIVED, Borrower hereby promises to pay to the order of Lender, at the office of Lender located at Mueller-Strasse 178, 13353 Berlin, Germany, Attention: Finance Department or at such other place as Lender may from time to time designate to Borrower in writing:

(i) the principal sum of FIFTEEN MILLION AND 00/100 (US$15,000,000.00) DOLLARS in currency of the United States of America, or, such lesser amount as shall then equal the aggregate unpaid principal balance of the Loans as may be due and owing under the Loan Agreement, payable in accordance with the provisions of the Loan Agreement, subject to acceleration upon the occurrence of an Event of Default under the Loan Agreement or earlier termination of the Loan Agreement pursuant to the terms thereof; and

(ii) interest on the principal amount of this Note from time to time outstanding until such principal amount is paid in full at the applicable Interest Rate in accordance with the provisions of the Loan Agreement. In no event, however, shall interest exceed the maximum interest rate permitted by law. Upon and after the occurrence of an Event of Default, and during the continuation thereof, interest shall be payable at the Default Rate.

This Note is the Note referred to in the Loan Agreement and is secured by the liens granted pursuant to the Security Agreement, is entitled to the benefits of the Loan Agreement and the other Loan Documents and is subject to all of the agreements, terms and conditions therein contained. This Note may be prepaid in whole or in part at any time without premium or penalty.

This Note may be assigned only in accordance with the Loan Agreement. This Note is not negotiable by Lender except to an Affiliate.

If an Event of Default under Section 7.10 of the Loan Agreement shall occur, then this Note shall immediately become due and payable, without notice, together with reasonable attorneys' fees if the collection hereof is placed in the hands of an attorney to obtain or enforce payment hereof. If any other Event of Default shall occur under the Loan Agreement or any of the Loan Documents, then this Note may, as provided in the Loan Agreement, be declared to be

immediately due and payable, without a notice period, together with reasonable attorneys' fees, if the collection hereof is placed in the hands of an attorney to obtain or enforce payment hereof.

This Note shall be governed by and construed and enforced in accordance with the laws of the State of New York.

Borrower expressly waives any presentment, demand, protest, notice of protest, or notice of any kind except as expressly provided in the Loan Agreement.

CANCELLED

RFIX MEDICAL, INC.,
Borrower

By: Michael D. Webb
Name: Michael D. Webb
Title: CEO

STATE OF Massachusetts
SS.:
COUNTY OF Middlesex

On the 23 day of May, 2003, before me personally came Michael Webb, to me known, who being by me duly sworn, did depose and say that he/she is the CEO of Rfix Medical, Inc., the Borrower described in and which executed the foregoing instrument; and that he/she signed his/her name thereto as the act and deed of such corporation by order of the board of directors of said corporation.

Barbara A Murphy
Notary Public

TRA 1796714v2

Commission Expires 5/21/04

2

APPENDIX II

U. S. Patent No. 6,676,929

US006676929B2

(12) **United States Patent**
McMurry et al.

(10) **Patent No.: US 6,676,929 B2**
(45) **Date of Patent: Jan. 13, 2004**

(54) **DIAGNOSTIC IMAGING CONTRAST AGENTS WITH EXTENDED BLOOD RETENTION**

(75) Inventors: **Thomas J. McMurry**, Winchester, MA (US); **Hironao Sijiki**, Gifu (JP); **Daniel M. Scott**, Acton, MA (US); **Randall B. Lauffer**, Brookline, MA (US)

(73) Assignee: **Epix Medical, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 114 days.

(21) Appl. No.: **10/034,522**

(22) Filed: **Dec. 20, 2001**

(65) **Prior Publication Data**

US 2002/0164289 A1 Nov. 7, 2002

Related U.S. Application Data

(63) Continuation of application No. 08/875,365, filed as application No. PCT/US96/00164 on Jan. 16, 1996, now abandoned, which is a continuation-in-part of application No. 08/382,317, filed on Feb. 1, 1995, now abandoned.

(51) **Int. Cl.**[7] **A61B 5/055**
(52) **U.S. Cl.** **424/9.364**
(58) **Field of Search** 424/9.364, 9.365, 424/9.36, 9.3

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Primary Examiner—Michael G. Hartley
(74) *Attorney, Agent, or Firm*—Fish & Richardson P.C.P.A.

(57) **ABSTRACT**

The present invention relates to contrast agents for diagnostic imaging with prolonged blood retention. In particular, this invention relates to novel compounds that are characterized by an image enhancing moiety (IEM); a protein plasma binding moiety (PPBM); and a blood half-life extending moiety (BHEM). This invention also relates to pharmaceutical compositions comprising these compounds and to methods of using the compounds and compositions for blood half-life extension and contrast enhancement of diagnostic imaging.

10 Claims, No Drawings

FOREIGN PATENT DOCUMENTS

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DIAGNOSTIC IMAGING CONTRAST AGENTS WITH EXTENDED BLOOD RETENTION

RELATED APPLICATION DATA

This application is a continuation of U.S. patent application Ser. No. 08/875,365, filed Dec. 12, 1997, now abandoned, which is a §371 application of International Patent Application No. PCT/US96/00164 (WO 96/23526), filed Jan. 16, 1996, which is a continuation-in-part of U.S. patent application Ser. No. 08/382,317, filed Feb. 1, 1995 now abandoned.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to contrast agents for diagnostic imaging. In particular, this invention relates to novel compounds which exhibit improved blood retention. The compounds comprise:

a) an image-enhancing (or signal-generating) moiety (IEM);

b) a plasma protein binding moiety (PPBM); and

c) a blood half-life extending moiety (BHEM). This invention also relates to pharmaceutical compositions comprising these compounds and to methods of using the compounds and compositions for blood half-life extension and contrast enhancement of diagnostic imaging.

BACKGROUND OF THE INVENTION

Diagnostic imaging techniques, such as magnetic resonance imaging (MRI), x-ray, nuclear radiopharmaceutical imaging, ultraviolet/visible/infrared light, and ultrasound, have been used in medical diagnosis for a number of years. In some cases, the use of contrast media to improve the image quality or provide specific information has been ongoing for many years. In other cases, such as imaging with light or ultrasound, the introduction of contrast media is imminent.

The contrast agent must interfere with the wavelength of electromagnetic radiation used in the imaging technique, alter the physical properties of tissue to yield an altered signal, or, as in the case of radiopharmaceuticals, provide the source of radiation itself. Commonly used materials include organic molecules, metal ions, salts or chelates, particles (particularly iron particles), or labeled peptides, proteins, polymers or liposomes. After administration, the agent may non-specifically diffuse throughout body compartments prior to being metabolized and/or excreted; these agents are generally known as non-specific agents. Alternatively, the agent may have a specific affinity for a particular body compartment, cell, organ, or tissue; these agents can be referred to as targeted agents.

For agents which are injected or absorbed into the body and distributed by the blood, it is desirable to have an appropriate blood half-life. While extremely long half-lives (i.e., days or weeks) are unnecessary in clinical imaging situations and possibly dangerous (due to the increased chance for toxicity and metabolic breakdown into more toxic molecules), short half-lives are also not desirable. If the image enhancement lasts for too short of time, it is difficult to acquire a high-quality image of the patient. In addition, rapid clearance of a targeted agent will reduce the amount of the agent available to bind to the target site and thus reduce the "brightness" of the target site on the image.

Increasing the blood half-life of an imaging agent involves interfering with one or more of the following clearance mechanisms:

1) Renal excretion. Molecules below 60,000 dalton molecular weight, particularly small molecules, can be removed from the blood by nonspecific glomerular filtration in the kidneys. If the molecules exhibit some degree of binding to plasma proteins or other constituents of blood, only the free fraction will be available for filtration and the rate of renal excretion will be reduced accordingly.

(2) Hepatocellular uptake. If a molecule possesses hydrophobic character, some fraction of the complex is taken up by liver cells and excreted into the bile. In general, the greater degree of hydrophobicity a molecule possesses, the greater the hepatocyte uptake rate. Though hydrophobicity also leads to plasma protein binding and a reduction in the apparent free concentration of the molecule, the hepatocellular uptake rate can still be very high (D. Sorrentino et al., *Prog. Liver Disease*, pp. 203–24 (1990)), thus reducing the blood half-life. Reduction in blood half-life may or may not be accompanied by an increase in the total hepatobiliary excretion, i.e., the fraction of the administered dose which eventually appears in the feces. The latter quantity is determined by many factors other than the hepatocellular uptake rate, including the extent of cytosolic protein binding inside the hepatocyte, the affinity for canalicular (hepatocyte-to-bile) transport systems, effects on bile flow and enterohepatic recirculation. Extension of blood half-life must be shown by blood or plasma sampling, not simply by measuring decreases in the total hepatobiliary excretion. Similarly, simply obtaining and measuring significant plasma protein binding of a contemplated contrast agent is not sufficient to show that its blood half-life is longer due to lower renal excretion.

3) Reticuloendothelial (RE) or other systems. Large molecular weight substances, such as liposomes, polymers, proteins, and particles, can be rapidly cleared from the blood by recognition (e.g., opsonization, or coating with proteins prior to cellular uptake) and uptake into cells, particularly the RE cells of the liver (the Kupfer cells), spleen and bone marrow.

Two general strategies have been reported to increase blood half-life for imaging agents. One way is to covalently attach the imaging agent via strong or metabolizable chemical bonds to a large molecular weight polymer, protein, liposome, or particle. For example, gadolinium diethylenetriamine-pentaacetic acid (Gd-DTPA) has been attached to human serum albumin (HSA), poly-L-lysine, or dextran (A. N. Oksendal et al., *J. Magn. Reson. Imaging*, 3, pp. 157–165 (1993); S. M. Rocklage, "Contrast Agents," *Magnetic Resonance Imaging*, Mosby Year Book, pp. 372–437 (1992)). This is done to reduce the rate of glomerular filtration in the kidneys and retain the agent in the blood. However, this can lead to long-term retention of the agent. In addition, the firmly bound imaging agents can potentially release toxic by-products such as free metal ions in the metabolism sites for the macromolecule. Furthermore, large conjugates may be difficult to target to specific sites in the body.

The second strategy has been applied to liposomes, polymers, proteins, and particles which are usually rapidly removed from the circulation by the RE system or by other means. The placement of long hydrophilic polymers, such as polyethyleneglycol (PEG), on the surface of the substance reduces uptake by the RE or other systems (C. Tilcock et al., *Biochimica et Biophysica Acta*, 1148, pp. 77–84 (1993); A. A. Bogdanoy et al., *Radiology*, 187, pp. 701–706 (1993)). It is hypothesized that the large, strongly hydrated polymer groups interfere with the molecular process required for recognition and uptake of the substances. The disadvantages of this strategy include: a) high cost and cumbersome manufacturing processes; b) lack of targetability of the large conjugates; and c) applicability appears to be limited to large molecular weight substances.

A particular challenge is for targeted small molecules which possess some lipophilic character. These can suffer from rapid hepatocellular uptake and blood clearance, possibly reducing the "brightness" at the target site. This is a particular problem where lipophilicity is required to achieve targeting to proteins or other biological targets.

A special case of this problem is the development of small molecule blood pool agents. Current small molecule non-specific agents, such as Gd-DTPA for MRI, have relatively fast clearance from the blood and are thus not optimal for imaging blood vessels (i.e., MR angiography) or for monitoring the blood flow into the heart, brain, tumors, or other organs or lesions. Lipophilic agents that target plasma proteins are known in the art. See U.S. Pat. Nos. 4,880,008 and 5,250,285. While these agents bind to plasma protein, in particular to human serum albumin, they can also be subject to rapid hepatocellular uptake and reduced blood half-life.

There remains a need for contrast agents that are retained by the blood for a prolonged period of time.

SUMMARY OF THE INVENTION

The present invention provides diagnostic imaging contrast agents which exhibit improved blood retention. The novel compounds comprise:

a) an image-enhancing (or signal-generating) moiety (IEM);

b) a plasma protein binding moiety (PPBM); and

c) a blood half-life extending moiety (BHEM).

This invention also relates to pharmaceutical compositions comprising these compounds and to methods of using the compounds and compositions for blood half-life extension and contrast enhancement of diagnostic imaging.

These contrast agents exhibit reduced rates of both renal and hepatocellular uptake and no apparent uptake by the RE system. The agents may be targeted to the blood pool or any other biological component. Since the agent is lost less rapidly from the bloodstream, lower doses can be used at a higher margin of safety. The approach is general to both large and small molecules.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

The term "specific affinity" or "molecular affinity" as used herein, refers to the capability of the contrast agent to be taken up by, retained by, or bound to a particular biological component to a substantially greater degree than other components. Contrast agents which have this property are said to be "targeted" to the "target" component.

The present invention relates to novel compounds which enhance the contrast in diagnostic imaging. These compounds comprise:

a) an image-enhancing (or signal-generating) moiety (IEM);

b) a plasma protein binding moiety (PPBM); and

c) a blood half-life extending moiety (BHEM). Diagnostic imaging includes, but is not limited to, MRI, x-ray, nuclear radiopharmaceutical imaging, ultraviolet/visible/infrared light, and ultrasound.

Image Enhancing Moiety ("IEM")

According to the present invention, the first domain, IEM, can be any chemical or substance which is used to provide the signal or contrast in imaging.

The signal enhancing domain can be an organic molecule, metal ion, salt or chelate, particle (particularly iron particle), or labeled peptide, protein, polymer or liposome.

A particularly useful IEM is a physiologically compatible metal chelate compound consisting of one or more cyclic or acyclic organic chelating agents complexed to one or more metal ions with atomic numbers 21–29, 42, 44, or 57–83.

For x-ray imaging, the IEM may consist of iodinated organic molecules or chelates of heavy metal ions of atomic numbers 57 to 83. Examples of suitable compounds are described in M. Sovak, ed., "Radiocontrast Agents," *Springer-Verlag*, pp.23–125 (1984) and U.S. Pat. No. 4,647,447.

For ultrasound imaging, the IEM consists of gas-filled bubbles such as Albunex, Echovist, or Levovist, or particles or metal chelates where the metal ions have atomic numbers 21–29, 42, 44 or 57–83. Examples of suitable compounds are described in Tyler et al., *Ultrasonic imaging*, 3, pp. 323–29 (1981) and D. P. Swanson, "Enhancement Agents for Ultrasound: Fundamentals," *Pharmaceuticals in Medical Imaging*, pp. 682–87 (1990).

For nuclear radiopharmaceutical imaging or radiotherapy, the IEM consists of a radioactive molecule. More preferred are chelates of Tc, Re, Co, Cu, Au, Ag, Pb, Bi, In, and Ga. Even more preferred are chelates of Tc-99m. Examples of suitable compounds are described in Rayudu GVS, *Radiotracers for Medical Applications*, I, pp. 201 and D. P. Swanson et al., ed., *Pharmaceuticals in Medical Imaging*, pp. 279–644 (1990).

For ultraviolet/visible/infrared light imaging, the IEM consists of any organic or inorganic dye or any metal chelate.

For MRI, the IEM consists of a metal-ligand complex of a paramagnetic form of a metal ion with atomic numbers 21–29, 42, 44, or 57–83.

In order to effectively enhance NMR imaging, the complex must be capable of enhancing the relaxation rates $1/T_1$ (longitudinal, or spin-lattice) and/or $1/T_2$ (transverse, or spin-spin) of water protons or other imaging or spectroscopic nuclei, including protons, P-31, C-13, Na-23, or F-19 on other biomolecules or injected biomarkers. Relaxivities R_1 and R_1 are defined as the ability to increase $1/T_1$ or $1/T_2$, respectively, per mM of metal ion; units are $mM^{-1}S^{-1}$. For the most common form of clinical MRI, water proton MRI, relaxivity is optimal where the paramagnetic ion bound to the chelating ligand still has one or more open coordination sites for water exchange (R. B. Lauffer, *Chemical Reviews*, 87, pp. 901–927 (1987)). However, this must be balanced with the stability of the metal chelate (vide infra) which generally decreases with increasing numbers of open coordination sites. More preferably, therefore, the complex contains only one or two open coordination sites.

In addition to increasing the $1/T_1$ or $1/T_2$ of tissue nuclei via dipole-dipole interactions, MRI agents can affect two other magnetic properties and thus be of use clinically:

1) an iron particle or metal chelate of high magnetic susceptibility, particularly chelates of Dy, Gd, or Ho, can alter the MRI signal intensity of tissue by creating microscopic magnetic susceptibility gradients (A. Villringer et al, Magn. Reson. Med. 6, pp. 164–174 (1988)). No open coordination sites on a chelate are required for this application.

2) an iron particle or metal chelate can also be used to shift the resonance frequency of water protons or other imaging or spectroscopic nuclei, including protons, P-31, C-13, Na-23, or F-19 on other biomolecules or injected biomarkers. Here, depending on the nucleus and strategy used, zero to three open coordination sites may be employed.

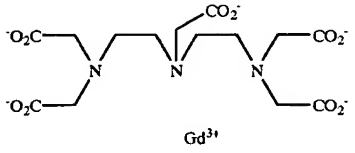
The preferred paramagnetic metal is selected from the group consisting of Gd(III), Fe(III), Mn(II and III), Cr(III), Cu(II), Dy(III), Tb(III), Ho(III), Er(III) and Eu(III). The most preferred is Gd(III).

Although the paramagnetic metal is used in a complexed form, toxic effects may still arise due to the dissociation of the metal ion from the complex. The organic chelating ligand should be physiologically compatible. The molecular size of the chelating ligand should be compatible with the size of the paramagnetic metal. Thus gadolinium (III), which has a crystal ionic radius of 0.938A, requires a larger chelating ligand than iron (III), which has a crystal ionic radius of 0.64A.

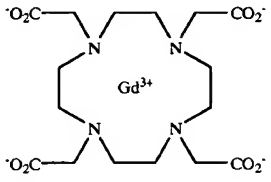
In general, the degree of toxicity of a metal chelate is related to its degree of dissociation in vivo before excretion. Toxicity generally increases with the amount of free metal ion. For complexes in which kinetic stability is low, a high thermodynamic stability (a formation constant of at least 10^{15} M^{-1} and more preferably at least 10^{20} M^{-1}) is desirable to minimize dissociation and its attendant toxicity. For complexes in which kinetic stability is comparatively higher, dissociation can be minimized with a lower formation constant, i.e., 10^{10} M^{-1} or higher.

Toxicity is also a function of the number of open coordination sites in the complex. The fewer coordination sites, the less tendency there is, generally, for the chelating agent to release the paramagnetic substance. Preferably, therefore, the complex contains two, one or zero open coordination sites. The presence of more than two open sites in general will unacceptably increase toxicity by release of the metal ion in vivo.

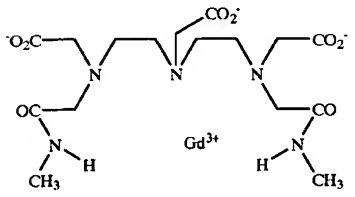
Many suitable chelating ligands for MRI agents are known in the art. These can also be used for metal chelates for other forms of biological imaging. For MRI imaging, the preferred IEMs include:



Magnevist
gadopentetate dimeglumine
DTPA

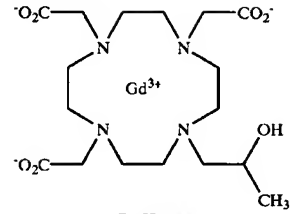


Dotarem
gadoterate meglumine
DOTA



Omniscan
gadodiamide
DTPA-BMA

-continued



ProHance
gadoteridol
HP-DO3A

Plasma Protein Binding Moiety ("PPBM")

According to the present invention, the second component of the contrast agents of this invention is a PPBM. This portion of the compound binds the contrast agent to plasma proteins and reduces the rate of renal excretion.

Plasma proteins of interest include albumin, particularly human serum albumin (HSA), which binds molecules possessing some lipophilic portions and either negative charges at physiological pH or partial negatively charged oxygens or sulphurs or fluorines; alpha acid glycoprotein, which binds primarily positively charged molecules; globulins, which bind steroidal molecules; and lipoproteins, which bind lipophilic or fatty acid-type molecules. The PPBM therefore must be selected properly to achieve the binding to the appropriate protein. Since HSA is present at the highest concentration in serum and has high affinity and capacity for binding a wide range of molecules, it is the preferred plasma protein to be used to increase blood half-lives. HSA is also the preferred plasma protein target because it binds to negatively charged molecules which tend to be less, toxic than positively charged molecules.

For binding to HSA, a wide range of hydrophobic or amphiphilic substances may be useful as the PPBM (U. Kragh-Hansen, *Pharm. Rev.*, 33, pp. 17–53 (1981); X. M. He et al., *Nature*, 358, pp. 209–215 (1992); D. C. Carter, *Adv. Protein Chem.*, 45, pp. 153–203 (1994)). These include but are not limited to aliphatic or aryl groups with 1 to 60 carbons as well as any number of nitrogens, oxygens, sulfurs, halogens, alkyl groups, amides, esters, and sulfonamides substituents. Alternatively, the PPBM may be a peptide containing hydrophobic amino acid residues and/or substituents with or without hydrophobic or hydrophilic termination groups. To obtain 10% binding in plasma, the preferred PPBM has at least 7 carbon atoms, more preferably 13, and most preferably 18 carbon atoms.

As stated above, for binding to HSA, a wide range of hydrophobic substances may be useful as the PPBM. In general, binding affinity to HSA and possibly other proteins will increase with the hydrophobicity of the PPBM. Theoretical estimates of the hydrophobicity of a substituent such as a PPBM can be obtained by calculating the contribution to the log of the octanol-water (or octanol-buffer) partition coefficient (log P) for the PPBM itself using the Hansch π constant for substituents. See A. Leo and C. Hansch, "Partition Coefficients and their Uses," *Chemical Reviews*, 71, pp. 525–616 (1971); K. C. Chu, "The Quantitative Analysis of Structure-Activity Relationships," Burger's *Medicinal Chemistry*, Part 1, pp. 393–418, (4th ed. 1980). Binding affinity will increase with increasing log P contributions. For example, for substituents on aliphatic groups, the following n constants can be used:

Group	π-aliphatic
CH_3	0.50
Phenyl	2.15

For substituents on aryl groups, the following n constants can be used:

Group	π-aliphatic
CH_3	0.56
CH_2CH_3	1.02
Phenyl	1.96

Thus, the log P contribution for a p-methylbenzyl group attached to an IEM would be calculated as follows (using the value of the π-aliphatic for CH_3 as an estimate for the $—CH_2—$ group):

log P contribution=0.50+2.15+0.56=3.21

In binding to HSA, a minimum log P contribution of 2 (equivalent to 4 CH_3 groups or one phenyl ring) is required to achieve significant binding. More preferred is a log P contribution of 3. Even more preferred is a log P contribution of 4.

HSA binding can be assessed by equilibrium dialysis or ultrafiltration using 4.5% weight/volume HSA in a pH 7.4 buffer. Preferably at least 10%, and more preferably at least 50%, more preferably at least 80%, and most preferably at least 95% of the contrast agent is bound to HSA at a physiological relevant concentrations (0.01–10 mM in plasma for MRI, x-ray, light, and ultrasound; <1 uM for radiopharmaceuticals). In this application, the measurement of percent binding of the contrast agent to HSA has an error of approximately +/–5%. Protein binding to other proteins or to serum can be assessed in a similar fashion.

The addition of lipophilic groups into a contrast agent is likely to decrease the solubility of the agent. To retain efficient solubility of the contrast agent at clinically effective dosage levels or higher, it may be preferred to incorporate one or more hydrogen-bonding groups (oxygen, nitrogens, etc.) into the PPBM.

While purely aliphatic groups can be used as PPBMs, these may not be as preferred as mixed aliphatic-aryl groups or purely aryl groups. Especially when a negative charge is attached to a purely aliphatic groups, particularly long and flexible ones, the contrast agent may interfere with the metabolism of endogenous molecules such as fatty acids or the interactions between membrane proteins and lipids. This may increase the toxicity of the agent. Thus it is preferred that the PPBM contain at least one aryl ring.

In the case of HSA-bound MRI agents for blood pool, tumor, or tissue enhancement, it is especially preferable for the contrast agent to contain two or more distinct lipophilic groups to fully immobilize the agent when bound to the protein. These groups may be on one PPBM, or as two or more separate chemical groups attached to the contrast agent. Because of their bulky nature and rigidity, it is preferable that the two or more groups each consist of an aromatic ring, with the two or more rings in the entire molecule arranged in a rigid, non-planar orientation.

The magnetic efficiency, or relaxivity, of a MRI agent is generally highest when the agent has a rotational correlation time approximately equal to HSA (R. B. Lauffer, *Chemical Reviews*, 87, pp. 901–927 (1987)). While a small molecule such as Gd-DTPA has a rotational correlation time of approximately 0.1 nanoseconds (nsec), HSA has a correlation time of greater than 5–10 nsec; if a chelate has this longer correlation time, the magnetic fluctuations between the paramagnetic ion and the water protons occur on the same time scale as the Larmor frequency, generating the most efficient longitudinal (T_1) relaxation possible and thus the highest possible relaxivity. Any flexibility of the chelate when bound to the protein is expected to decrease the effective rotational correlation time and thus decrease relaxivity. Since one site of attachment to the protein may still yield flexibility in several directions, additional sites of attachment may be preferred.

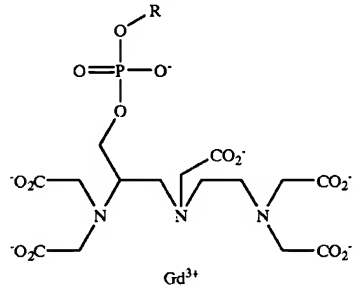
The degree to which an agent has been tuned for maximum relaxivity can be assessed by measuring the relaxivity-bound (R_1-bound) in the presence of HSA. This requires measuring the relaxivity of the free chelate (R_1-free) as well as the relaxivity (R_1-observed) and per cent binding of the agent in 4.5% HSA. The R_1-observed is a mole fraction weighted average of R_1-free and R_1-bound:

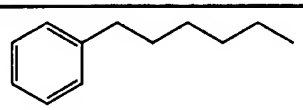
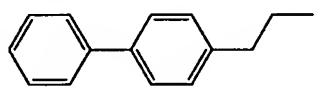
$$R_1\text{-observed}=(\text{fraction-free}*R_1\text{-free})+(\text{fraction-bound}*R_1\text{-bound})$$

Thus:

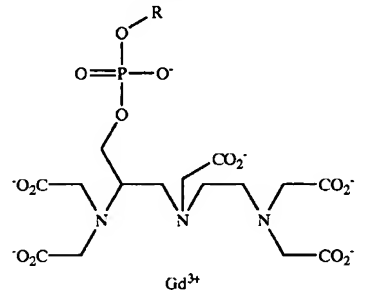
$$R_1 - \text{bound} = \frac{[R_1 - \text{observed} - (\text{fraction} - \text{free} * R_1 - \text{free})]}{\text{fraction} - \text{bound}}$$

The benefit of having two or more aryl rings held in a rigid, non-planar fashion can be seen in the following table which shows relaxivity-bound values for MS-322 (56 $mM^{-1}s^{-1}$) and MS-325 (42 $mM^{-1}s^{-1}$) versus MS-317 (34 $mM^{-1}s^{-1}$). The biphenyl or diphenyl groups of MS-322 and MS-325 appear to be restricting the mobility of the HSA-bound contrast agent. In this application, the error associated with the measurement of relaxivity-bound values is approximately +/–5%.

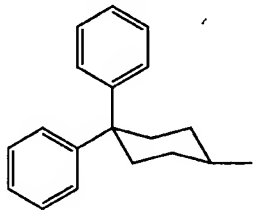


R	R_1-bound, $mM^{-1}s^{-1}$
MS-317 	34
MS-322 	56

-continued



R	R_1-bound, $mM^{-1}s^{-1}$
MS-325	42



As can be seen in the above table, compounds having two rings rigidly held in a non-planar orientation had higher relaxivity-bound values.

As can be seen in the above equations, the actual R_1-observed can be increased by increasing the fraction-bound, that is, increasing the binding affinity of the agent to HSA. This may also lead to lower renal excretion and longer blood half-lives and is thus synergistic. Nevertheless, in order to use the lowest dose and have the highest margin of safety, it is still important to maximize the potency of the agent by maximizing R_1-bound.

Blood Half-Life Extending Moiety ("BHEM")

The third domain of the contrast agents of this invention, the BHEM, reduces the rate of hepatocyte uptake of the contrast agent. The balance of hydrophilicity and lipophilicity and the exact molecular structure of a molecule determine its hepatocyte uptake rate.

In the contrast agents of this invention, the BHEMs of this invention reduce or eliminate hepatocyte uptake without unduly interfering with the efficacy of the PPBM. The BHEMs are extremely hydrophilic groups which can hydrogen-bond with water. The presence on a contrast agent of the hydrophilic BHEM reduces the hepatocyte uptake of the agent.

Examples of chemical groups which would serve as a BHEM include carbon, phosphorous, tungsten, molybdenum, or sulfur atoms having attached charged or neutral heteroatoms such as oxygen, nitrogen, sulfur or halogens (especially fluorine) possessing two or more lone electron pairs (i.e., full or partial negative charge) or electropositive hydrogen atoms (i.e., protonated amine) for hydrogen bonding with water. These include groups such as sulfone, ether, urea, thio-urea, amine, sulfonamide, carbamate, peptide, ester, carbonate and acetals. Preferred groups include those which possess one or more partial or full negative charges in aqueous solution at physiological pH wherein the negatively charged atoms cannot be partially or fully neutralized by covalent or coordinate covalent bonding to the IEM. Examples of these preferred BHEMs include negatively charged groups such as phosphate mono-ester, phosphate diester, carboxylate, and sulphonate. More preferred are those which have phosphate groups or any ester forms thereof. Even more preferred are phosphate diesters, since: a) they are highly hydrophilic with four hydrogen-bonding oxygens; b) they are relatively readily synthesized using techniques shown below; c) they serve as excellent linkers between the IEM and the PPBM; and d) because phosphate compounds exist and are metabolized naturally in the body, phosphate diester-containing contrast agents are expected to be non-toxic.

All of the above groups may in turn be attached to a linker moiety linking them to either the IEM, the PPBM, or both. A linker moiety is any physiologically compatible chemical group that does not interfere with the functions of the IEM, PPBM, or BHEM. Preferred linkers are synthetically easy to incorporate into the contrast agent. They are also not so unduly large as to manifest their own undesired biological function or targeting influence onto the contrast agent. Preferably, the length of the linker is between 1 and 50 angstroms, more preferably 1 and 10 angstroms.

The incorporation into a contrast agent of this invention of a BHEM results in prolonged blood retention of the agent. Blood retention is preferably measured by calculating, in a rat plasma pharmacokinetic experiment, the area under the plasma concentration versus time curve ("Area Under the Curve" or "AUC-conc.") for a specific length of time (e.g., 0–10 minutes, 0–30 min., 0–60 min., 0–120 min., or 0-infinity). Blood retention (as measured by AUC-conc) can be evaluated experimentally by administration of a contrast agent to rats, rabbits, or higher mammals. It has been observed that blood half-life extension is greater in rabbits and higher mammals than in rats. In this application, blood half-life data, as measured by AUC-conc., represents experimentation in rats. The error associated with this data is approximately +/−10%.

The reason that a half-life measurement itself is not used is that the mathematical definition of this quantity is often not clear and the resulting estimates are variable depending on the pharmacokinetic model used and the length of time the blood samples were obtained.

For example, the average plasma concentrations observed after tail vein injection of 0.1 mmol/kg of Gd^{153}-labeled Gd-DTPA in two rats, using the Macintosh program KaleidaGraph, this AUC-conc. from 0 to 10 minutes was calculated as 3.5 mM min.

The contrast agents of this invention exhibit an AUC-conc. increase of at least 20% when the BHEM is added to the IEM and PPBM. They preferably exhibit an AUC-conc. increase of at least 40%, more preferably at least 70% and even more preferably at least 100%. In general, the increase in AUC-conc. caused by a BHEM is greater when the binding in plasma is significant, e.g., 20%–50% or greater. The calculated percent increase in AUC-conc. may be different for AUC-conc.'s determined over different time periods. Generally, the percent increase in AUC-conc. caused by the BHEM is greater for AUC-conc.'s taken over longer periods, e.g, 0–30 min., rather than 0–10 min.

Since the structure and physical characteristics of the entire contrast agent molecule will govern its binding in plasma, it is important to select IEMs and t BHEMs that are compatible with the desired binding. For example, to achieve binding to the positively charged binding sites on HSA, it is preferred to have IEMs and BHEMs of net neutral or net negative charge to reduce the possibility of repulsion and perhaps even increase binding affinity. For binding to alpha acid glycoprotein, at least some portion of the contrast agent should be positively charged. For binding to globulins, at least some portion of the contrast agent should be steroidal in nature. For binding to lipoproteins, at least some portion of the contrast agent should be lipophilic or fatty acid-like.

The contrast agents of the present invention fall generally into three categories:

1) Blood pool agents. When the binding affinity to plasma proteins is high (i.e., greater than 50% bound, or preferably greater than 80% bound, or more preferably greater than 95% bound), the agents tend to act primarily as blood pool agents. While the agents can access the interstitial space (the extracellular space in between cells) outside blood capillaries, generally the concentration of relevant plasma proteins such as HSA are lower in that space compared to plasma. Thus, the plasma concentration of the agents is higher than the interstitial concentration, and therefore structures in the body such as blood vessels or tissues containing a large amount of blood vessels are enhanced more than structures with low blood content. The applications for this type of agent include angiography (imaging of blood vessels), perfusion (determining the rate of blood flow into a tissue or tumor using rapid imaging), and blood volume determinations (e.g., to distinguish malignant tumors with good blood supply from benign tumors with lower blood volume). 2) Tissue- or tumor-enhancement agents. In some cases it is desired to allow the contrast agent to rapidly access the interstitial space and bind to plasma proteins there. For example, in MRI it may be desired to get the greatest possible enhancement from a tissue or tumor as soon as possible after injection. Since protein-bound MRI agents yield greater enhancement than free agents, the best agent would be one which can enter the interstitial space and bind to proteins. However, if the agent is highly bound in plasma, say greater than 95% bound, its transfer rate across the capillaries (determined by the free concentration) is too slow, and very little of the agent gets into the interstitial space and produces signal enhancement of tissue. Likewise, if the binding is only 10%, then the agent is free to enter the interstitial space but has little signal-enhancing power. Thus, a proper balance of transfer rate and binding affinity is required. For these applications, the binding of the agents in plasma should be greater than 10% and less than 95%, or preferably greater than 50% and less than 95%.

This approach is particularly useful in tumor imaging with MRI. Malignant tumors often have better blood flow than benign tumors, and thus rapid imaging of tumor (and interstitial) uptake can often distinguish these tumor types. However, for clinical application, one needs the greatest signal difference between the two tissues to allow clearer discrimination. The signal enhancement via protein binding will help in this regard. In addition, the new, rapidly growing capillaries of malignant tumors are leaky, leading to a higher concentration of plasma proteins in the interstitial space of these tumors. This may lead to greater signal enhancement in the malignant tumors compared to benign tumors with less leaky capillaries.

3) Targeted agents. When the agent is targeted to a specific tissue or lesion in the body, a similar logic as that described in the two paragraphs above applies. The relative affinities of the agent for plasma proteins and the target site needs to be balanced such that the agent has some access to bind to the target and at the same time has some binding to plasma proteins to increase blood half-life. For targeted applications, the binding of the agents in plasma should be greater than 10% and less than 95%, or preferably greater than 50% and less than 95%.

The targeting moiety may be a lipophilic substance, receptor ligand, antibody, or other biomolecule that is known to concentrate in the specific biological component desired to be imaged.

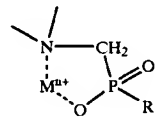
Structural Positioning

It is contemplated that the three moieties of the contrast agents of this invention can be arranged in a variety of positions with respect to each other. However, the position of the moieties may not be such that one moiety interferes with the intended function of the other. For example, in an HSA-binding contrast agent the placement of the BHEM should not block the ability of the PPBM to bind the agent to HSA. Since the major binding sites in HSA are sock-like (X. M. He et al., *Nature*, 358, pp. 209–215 (1992); D. C. Carter, *Adv. Protein Chem.*, 45, pp. 153–203 (1994)), with hydrophobic interiors (especially near the "toe" region) and positively charged "ankle" regions, the binding affinity of a PPBM would decrease if the distal portion of the PPBM were made extremely hydrophilic. As an illustrative example, if the PPBM is a phenyl ring, the most preferred BHEM position on the ring is ortho, followed by meta. A hydrophilic group in the para position would reduce the PPBM's binding affinity to HSA.

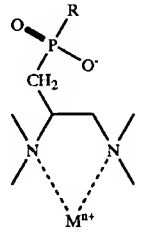
For IEMs that consist of a metal chelate, it is preferred that the BHEMs and PPBMs not be attached to the IEM so as to significantly reduce the strength of the binding between the metal ion and chelating ligand. For example, where the chelating arm is acetate, the BHEM or PPBM is preferably not attached to the acetate oxygen.

Another positional requirement is that the BHEM's negatively charged atoms cannot be partially or fully neutralized by covalent or coordinate covalent bonding to the IEM; this ensures that in aqueous systems the very hydrophilic atoms of the BHEM will be highly solvated. For example, when the IEM is a metal chelate, it is important to position the negatively charged atoms of the BHEM so that they cannot become neutralized by the positively charged metal ion (M^{n+}) of the IEM through coordinate covalent bonding via the formation of 5- or 6-membered chelate rings, the most stable ring sizes. Since 5-membered chelate rings are the most stable for the metal ions of interest for IEMs (such as gadolinium), it is most important to prevent their formation. Thus, as shown in the drawing below, a phosphinate (—PO_2—) or phosphonate (—PO_3—) BHEM cannot be attached to the nitrogen atom of an aminocarboxylate chelating agent via a —CH_2— linker since this will form a very stable 5-membered chelate ring. Similarly, a phosphodiester (—OPO_3—) BHEM should not be attached to the nitrogen atom of an aminocarboxylate chelating agent via a —CH_2— linker since this could form a 6-membered chelate ring. However, both of these BHEMs can be attached to other positions, such as the ethylene backbone of the ligand. In some cases, as shown, it may be preferred to increase the length of the linker group to make certain that 5- or 6-membered rings cannot form.

Phosphinate BHEM

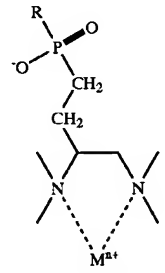


Strongly disfavored
(5-membered chelate ring,
charge neutralized)

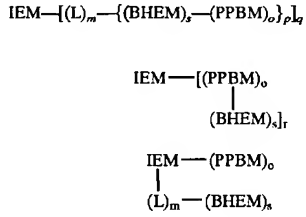


Disfavored
(6-membered chelate ring,
charge neutralized)

-continued

Phosphinate BHEM	
	More preferred (no possibility of 5- or 6-membered chelate rings or charge neutralization)

It is contemplated that the moieties of this invention can be positioned in the contrast agent so that the following structures may result:



(1)

(2)

(3)

wherein

IEM an image-enhancing moiety,

L is a linker moiety,

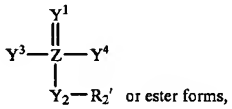
BHEM is a blood half-life extending moiety,

PPBM is a plasma protein binding moiety,

m can be equal to 0–4,

s, o, and p can be the same or different and equal to 1–4, and r and q are at least one.

If the moieties of this invention are positioned in the contrast agent as in structure (1) above, the BHEM is preferably sulfone, urea, thio-urea, amine, sulfonamide, carbamate, peptide, ester, carbonate, acetals and more preferably



where

Z=P, W, Mo, or S

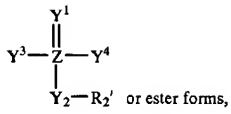
Y^1, Y^2=O or S

Y^3, Y^4=O, S or not present

R_2'=H, C_{1-6} alkyl or not present.

Most preferably, the BHEM is a phosphate group.

If the moieties of this invention are positioned in the contrast agent as in structure (2) above, the BHEM is preferably sulfone, urea, thio-urea, amine, sulfonamide, carbamate, peptide, ester, carbonate, acetals and more preferably the BHEM has the following formula:



where

Z=P, W, or Mo

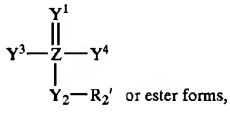
Y^1, Y^2=O or S

Y^3, Y^4=O, S or not present

R_2'=H, C_{1-6} alkyl or not present.

Most preferably, the BHEM is a phosphate group.

If the moieties of this invention are positioned in the contrast agent as in structure (3) above, the BHEM is preferably SO_3^- or ester forms, sulfone, urea, thio-urea, amine, sulfonamide, carbamate, peptide, ester, carbonate, acetal and more preferably



where

Z=P, W, Mo, or S

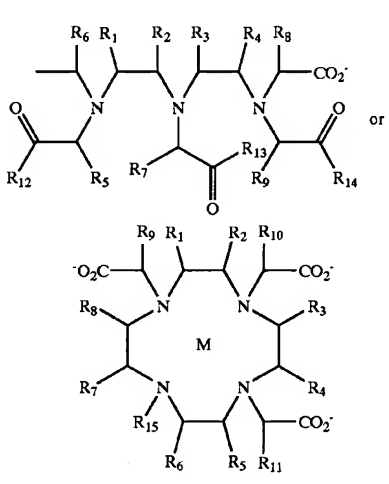
Y^1, Y^2=O or S

Y^3, Y^4=O, S or not present

R_2'=H, C_{1-6} alkyl or not present.

Most preferably, the BHEM is a phosphate group.

It is contemplated that if the moieties of this invention are positioned in the contrast agent as in structure (3) above, preferred contrast agents have the formulas:



where M is a metal ion with an atomic number of 21–29, 42, 44 or 57–83,

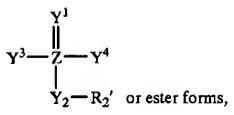
where R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{16} can be the same or different and selected from the group consisting of H, PPBM, BHEM and C_{1-6} alkyl, provided that at least one of these Rs is PPBM and at least another is BHEM,

R_{12}, R_{13} and R_{14} can be the same or different and selected from the group consisting of O^- and N(H) R_{17},

R_{15}=H, $CH_2CH(OH)CH_3$, hydroxy alkyl or CH (R_{16}) COR_{12} and

R_{17}=H or C_{1-6} alkyl.

For contrast agents comprising the formulas shown above, the metal ion M is more preferably Gd(III), Fe(III), Mn(II), Mn(III), Cr(III), Cu(III), Dy(III), Tb(III), Ho(III), Er(III) or Eu(III), and most preferably Gd(III). The BHEM is preferably sulfone, ether, urea, thio-urea, amine, amide, sulfonamide, carbamate, peptide, ester, carbonate, acetal and more preferably COO^- or ester forms, SO_3^- or ester forms and



or ester forms,

where

Z=P, W, Mo, or S

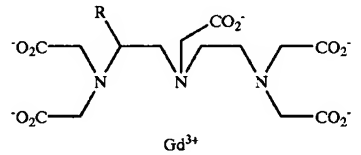
Y^1, Y^2=O or S

Y^3, Y^4=O, S or not present

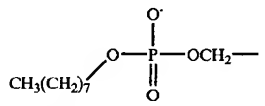
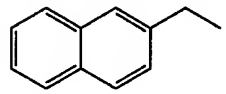
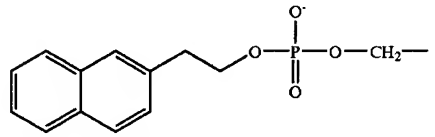
R_2'=H, C_{1-6} alkyl or not present.

In the case of an HSA-binding contrast agent, the BHEM may be placed in between the IEM and the PPBM as shown above in structure (1) or on the IEM away from the PPBM as shown above in structure (3). In this manner the full binding potential of the hydrophobic PPBM group can be expressed without interference from the hydrophilic BHEM group.

The following two pairs of examples serve to show the benefits of a phosphate BHEM inserted in between the IEM Gd-DTPA and two different PPBMs, an octyl C_8 aliphatic group and a naphthylmethyl group. Rats were injected intravenously (tail vein) with 0.1 mmol/kg of the Gd^{153} radiolabeled complexes. Plasma concentrations were determined over 30 minutes and fit to a standard bi-exponential two-compartment model. Results for the elimination half-life are shown as well as the area under the plasma concentration versus time curve (AUC-conc.) for the first 10 minutes. In addition, the $1/T_1$s of the plasma samples were recorded (at 20 MHZ, 37 deg. C.) to assess the efficacy as MRI agents. These values were expressed as area under the $1/T_1$ versus time curve (AUC-$1/T_1$) for the first 10 minutes.



Gd^{3+}

Cmpd	R	% bound to HSA	$t_{1/2}$, min	AUC-conc mM * min	AUC-$1/T_1$ s^{-1} * min
DTPA	H	0	15.0	3.5	27
MS-301	CH_3—$(CH_2)_7$—	44	6.2	2.7	59
MS-315		56	14.0	3.4	87
MS-310		30	6.8	1.8	29
MS-321		40	14.0	3.2	54

As shown in the above table, the addition of a phosphate BHEM to MS-301 and MS-310 (resulting in MS-315 and MS-321, respectively) increased the blood half-life of the contrast agent (as measured by AUC-conc.) by 26% and 78%, respectively.

The IEM Gd-DTPA is relatively hydrophilic and exhibits little or no binding to HSA. Thus, its relaxivity in plasma is not optimized and its ability to alter the $1/T_1$ (and blood signal on MRI) over time is limited (see the relatively low AUC-$1/T_1$ value). This is despite its relatively long blood half-life of 15 minutes.

To improve the HSA binding and relaxivity, a C_8 octyl group can be placed on the 1-position of the DTPA backbone. While this does impart HSA binding to the chelate and some improvement in blood signal, the lipophilic group alone leads to a much-shortened plasma half-life. The insertion of the phosphate-based BHEM actually enhances HSA binding and restores the plasma half-life to a value close to Gd-DTPA. As a result, the blood signal is considerably improved.

The proper placement of the BHEM in these examples shows the importance of this aspect of the invention. The addition of strongly hydrophilic groups to MS-301 or MS-310 enhanced binding to some degree. The placement of the phosphate groups in MS-315 and MS-321 between the IEM and the PPBM may allow the full hydrophobic surface of the PPBMs to interact with the interior of the HSA sites and at the same time create new beneficial interactions (e.g., electrostatic or hydrogen-bonding) between the compound and the "ankle" region of the HSA sites. In particular, it is possible that the negatively-charged phosphate groups are positioned well to interact with the positively-charged residues that line the "ankle" region.

As indicated above, the percentage increase in AUC-conc. can depend on the time for which measurements are made. For example, the addition of the phosphate BHEM onto MS-310 to make MS-321 increased the AUC-conc. for 0–10 min. from 1.8 to 3.2 mM min., a 78% increase. However, the AUC-conc. for 0–30 min. increased from 2.46 to 5.57 mM min., a 126% increase.

The following contrast agents are made:

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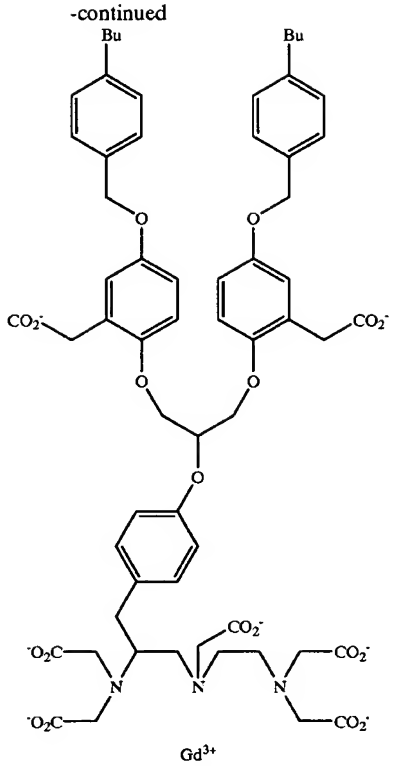

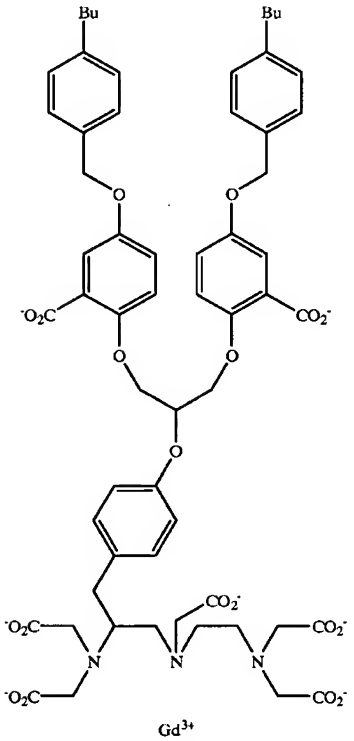

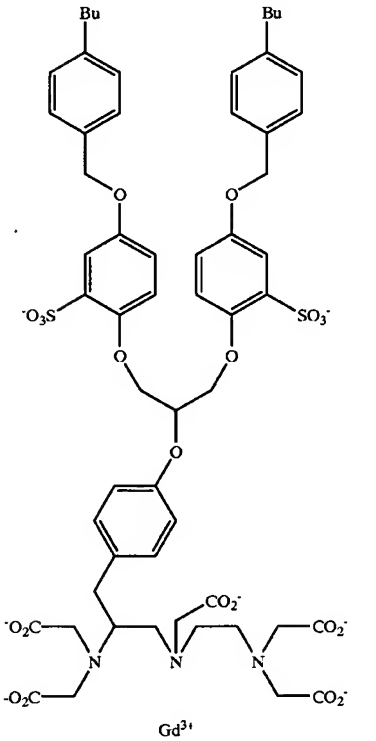

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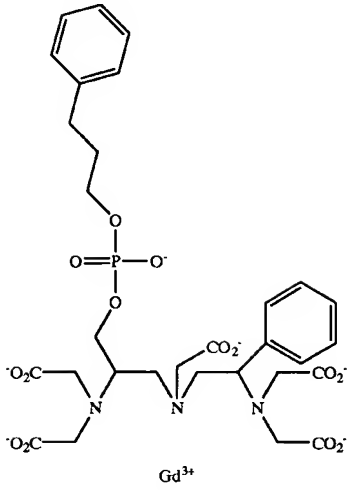
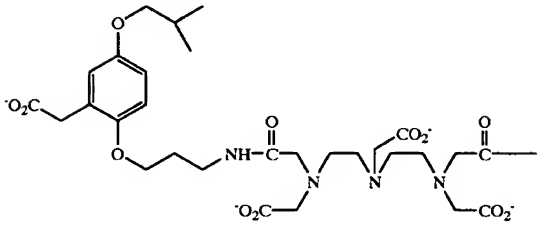


Gd^{3+}



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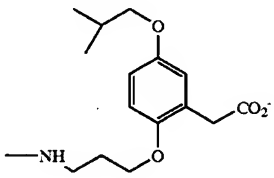
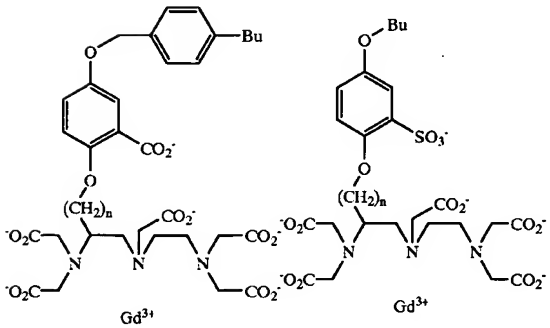
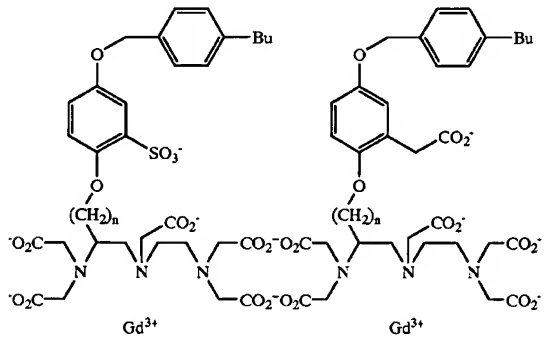




Gd^{3+} Gd^{3+}



Gd^{3+} Gd^{3+}

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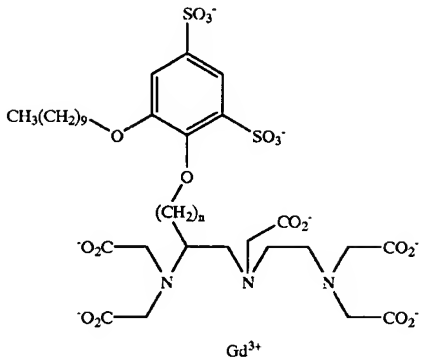
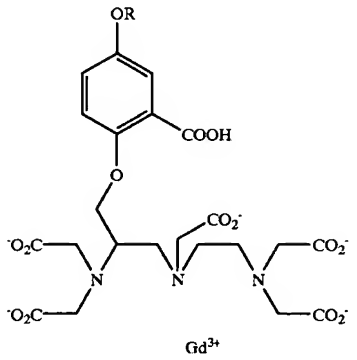
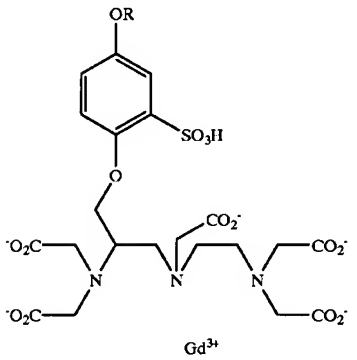


Gd^{3+}

In the above agents, n can be equal to 1–4.



Gd^{3+}

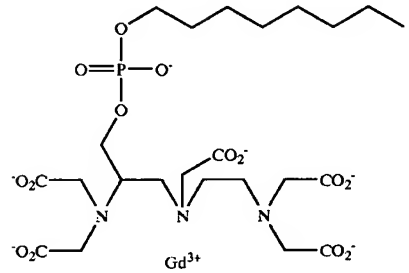


Gd^{3+}

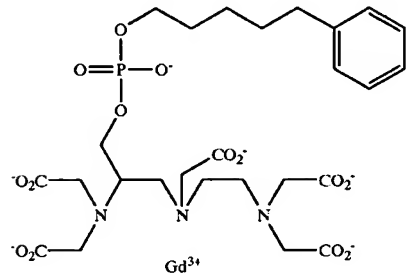
wherein R comprises an aliphatic group and/or at least one aryl ring, or comprises a peptide containing hydrophobic amino acid residues and/or substituents with or without hydrophobic or hydrophilic termination groups.

The preferred contrast agents of this invention are:

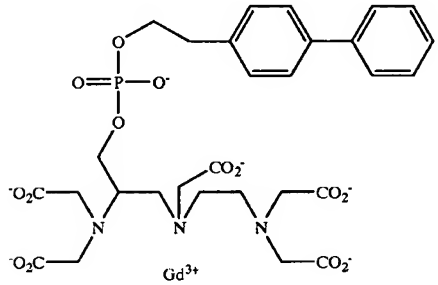
MS-315



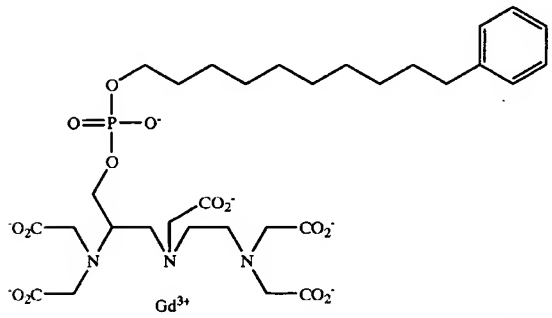
MS-317



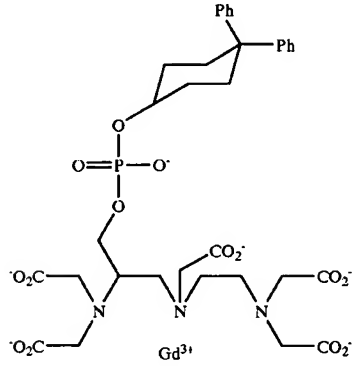
MS-322



MS-323



MS-325



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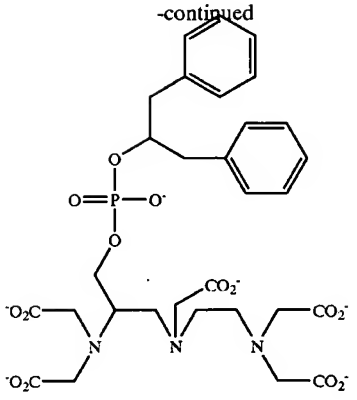
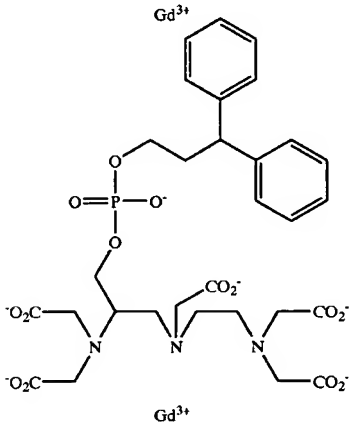
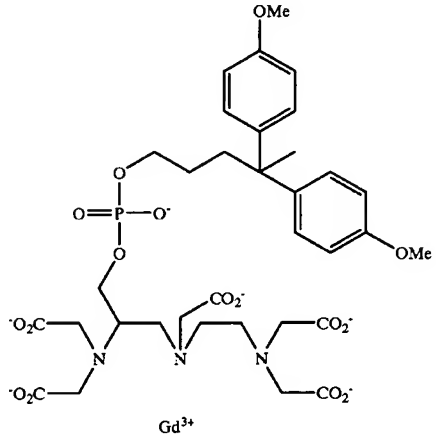
MS-326



MS-327



MS-328



The more preferred contrast agents of this invention are MS-317, MS-322, MS-325 and MS-328. The most preferred is MS-325.

Additional Properties of the Contrast Agents

Since different chiral forms of drugs or biomolecules can influence their performance in vivo, the same is likely to be true of the contrast agents of this invention. For every given chiral center, one form may have higher relaxivity, blood half-life, lower toxicity, fewer metabolites, or some other advantage or combination of these advantages. These chiral forms will be preferred.

To facilitate administration and uptake, the contrast agents of the present invention should have good water solubility. Preferably, the contrast agents are soluble to a

concentration of at least 1.0 mM, and preferably 10 mM, and more preferably 100 mM in water at room temperature.

For injection, the formulated agents should have only moderate viscosity to allow for rapid, convenient injections. The viscosity should be less than 10 centipoise, or preferably less than 5 centipoise, or more preferably less than 2 centipoise.

For injection, the formulated agents should also not have excessive osmolality, since this can increase toxicity. The osmolality should be less than 3000 milliosmoles/kg, or preferably less than 2500 milliosmoles/kg, or most preferably less than 900 milliosmoles/kg.

Use of the Contrast Agents

It is also contemplated that the IEM may comprise a pharmaceutically acceptable salt. Pharmaceutically acceptable salts of this invention include those derived from inorganic or organic acids and bases. Included among such acid salts are the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate and undecanoate. Base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, alkaline earth metal salts, such as calcium, magnesium and zinc salts, salts with organic bases, such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, and so forth. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates, such as dimethyl, diethyl, dibutyl and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides, such as benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. The preferred salts of this invention are the N-methyl-D-glucamine, calcium and sodium salts.

The pharmaceutical compositions of this invention comprise any of the complexes of the present invention, or pharmaceutically acceptable salts thereof, together with any pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, TRIS (tris(hydroxymethyl)amino-methane), partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

According to this invention, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

Since the contrast agents of this invention bind to plasma proteins, in some cases depending on the dose and rate of injection, the binding sites on plasma proteins may become saturated. This will lead to decreased binding of the agent and could compromise half-life or tolerability. Thus, it may be desirable to inject the agent pre-bound to a sterile albumin or plasma replacement solution. Alternatively, an apparatus/syringe can be used that contains the contrast agent and mixes it with blood drawn up into the syringe; this is then re-injected into the patient.

The compounds and pharmaceutical compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoirin dosage formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

When administered orally, the pharmaceutical compositions of this invention may be administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

Alternatively, when administered in the form of suppositories for rectal administration, the pharmaceutical compositions of this invention may be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

As noted before, the pharmaceutical compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the com-

pounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical compositions may be formulated in an ointment such as petrolatum.

For administration by nasal aerosol or inhalation, the pharmaceutical compositions of this invention are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Dosage depends on the sensitivity of the diagnostic imaging instrumentation, as well as the composition of the contrast agent. For example, for MRI imaging, a contrast agent containing a highly paramagnetic substance, e.g., gadolinium (III), generally requires a lower dosage than a contrast agent containing a paramagnetic substance with a lower magnetic moment, e.g., iron (III). Preferably, dosage will be in the range of about 0.001 to 1 mmol/kg body weight per day of the active metal-ligand complex. More preferably, dosage will be in the range of about 0.005 and about 0.05 mmol/kg body weight per day.

It should be understood, however, that a specific dosage regimen for any particular patient will also depend upon a variety of factors, including the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician.

If the application of this invention is MRI imaging, following administration of the appropriate dosage of the contrast agent, MRI imaging is carried out. The choice of pulse sequence (inversion recovery, IR; spin echo, SE, echo planar, EPI; time-of-flight, TOF; turbo-flash; gradient echo, GE) and the values of the imaging parameters (echo time, TE; inversion time, TI; repetition time, TR; flip angel, etc.) will be governed by the diagnostic information sought. In general, if one desires to obtain T_1-weighted images, then TE should be less than 30 milliseconds (or the minimum value) to maximize T_1-weighting. Conversely, if one desires to measure T_2, then TE should be greater than 30 milliseconds to minimize competing T_1 effects. TI and TR will remain approximately the same for both T_1- and T_2-weighted images; TI and TR are generally on the order of about 5–1000 and 2–1000 milliseconds, respectively.

The MRI contrast agents of the present invention are useful for general imaging of tumors, blood-brain-barrier breakdown, and other lesions. In addition they are very useful for examining perfusion, i.e., the blood flow into and out of tissues (heart, brain, legs, lungs, kidneys, tumors, etc.), and blood vessels (MR angiography). In addition, the agents can be used to enhance the signal changes in the brain during cognitive events (functional MRI).

It is contemplated that the contrast agents of the present invention may also be used to enhance diagnostic X-ray imaging as well as ultrasound and light imaging. In these cases, the doses of the agent will be approximately equal to that in MRI (0.001–10 mmol/kg). For nuclear imaging, however, the doses will be at tracer levels. For all of these techniques, the use and administration of contrast agents and the settings on the imaging machines is known in the art or uses commonly accepted principles.

In order that this invention may be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE

Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. THF was distilled from potassium benzophenone ketyl immediately prior to use. Methylene chloride was distilled over calcium hydride. All column chromatography was carried out under nitrogen by flash method described by Still with silica gel (230–400 mesh, EM Separation). All reactions were monitored by thin layer chromatography (TLC) performed on aluminum-backed silica gel 60 F_{254}, 0.2-mm plates (EM Separation), and compounds were visualized under UV light (254 nm), Ninhydrin-Plus reagent or Dragendorff's reagent (both Alltech) subsequent heating. Routine proton NMR spectra were recorded at 300 MHZ in $CDCl_3$ with TMS as internal standard, except for the spectra recorded in D_2O. Coupling constants (J) are reported in Hertz (Hz). ^{31}P NMR spectra were obtained at 121.4 MHZ.

Preparation of Phosphoramidite Intermediate

A. Serine Ethylenediamine Amide

Serine methyl ester hydrochloride (36.03 g, 232 mmol) was dissolved in 400 mL ethylenediamine and was stirred at room temperature for 16 hours. The ethylenediamine was removed by evaporation at reduced pressure. The residue was dissolved in 80 mL 4 N NaOH and was concentrated under reduced pressure. This material was dissolved in methanol (150 mL), filtered and concentrated twice. This residue was suspended in methylene chloride (150 mL) and methanol (5–10 mL) was added with heating until the oily residue was dissolved. The solution was dried over Na_2SO_4, filtered through celite and concentrated. The viscous oily product was carried on without further purification.

B. 2-Hydroxymethyldiethylenetriamine Trihydrochloride

The crude amide (<230 mmol) was dissolved in 100 mL THF. Borane.THF (1150 mL, 1.0 M) was added slowly to the stirred solution. The reaction was then refluxed under Ar for 16 hours. The excess borane was quenched by careful addition of 250 mL methanol at 0° C. The reaction mixture was concentrated under reduced pressure. Concentrated HCl (100 mL) was added slowly with cooling and the solution was then refluxed for 24 hours. The product mixture was concentrated under reduced pressure and was crystallized from MeOH/EtOH. This yielded 39.92 g of white solid (71% from methyl ester).

C. 1-Hydroxymethyl-DTPA-penta-t-butyl Ester (1)

To a solution of the hydroxymethyl diethylenetriamine trihydrochloride (30.25 g, 124.70 mmol) and diisopropylethylamine (218 ml, 1.25 mol) in 300 ml of dry DMF at room temperature under N_2 was added t-Butyl bromoacetate (126 ml, 0.78 mol) and stirred for 24 hours at room temperature. Solvents were then evaporated in vacuo and the residue was dissolved in EtOAc and extracted with H2O, NaHCO3 (sat), H2O and NaCl (sat). The residue was purified by silica gel column chromatography ($CHCl_3$ only—$CHCl_3$:MeOH=100:1) to give the pure product (oil, 70.12 g, 81.7%): Rf ($CHCl_3$:MeOH=10:1) 0.54,

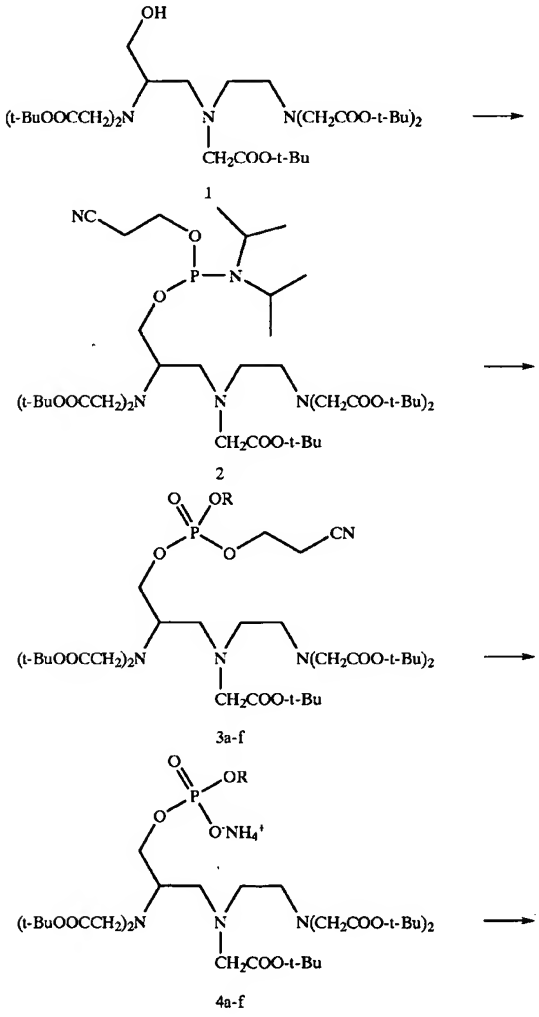
(ether:hexanes=2:1) 0.23; ^{1}H-NMR ($CDCl_3$) d 1.44 (brs, 45H), 2.44–3.06 (m, 6H), 3.24 and 3.29 (each d, each 1H, J=16.8), 3.34–3.58 (m, 10H), 3.66 (dd, 1H, J=11.2, 5.3), 4.20–4.70 (br, 1H).

D. Phosphoramidite Intermediate (2)

To a stirred solution of the penta t-butyl ester (1) (12.88 g, 18.72 mmol) and diisopropylethylamine (4.55 g, 36 mmol) in dist. CH_2Cl_2 (100 ml) was added 2-cyanoethyl N,N-diisopropylchlorophosphoramidite (5.92 g, 25 mmol) at room temperature. The mixture was stirred at room temperature for 2 hours, the solution was diluted with 100 ml of CH_2Cl_2 and washed with ice-cold 10% $NaHCO_3$ solution (100 ml), H_2O (100 ml), and brine (100 ml) and dried over $MgSO_4$. The organic layer was evaporated to afford crude product as a pale yellow oil (2). This crude oil can be used for the next coupling reaction without further purification.

Examples 1–6 below show the synthesis of some of the preferred contrast agents of this invention according to the following generalized scheme:

Synthesis of Phosphodiester Ligands



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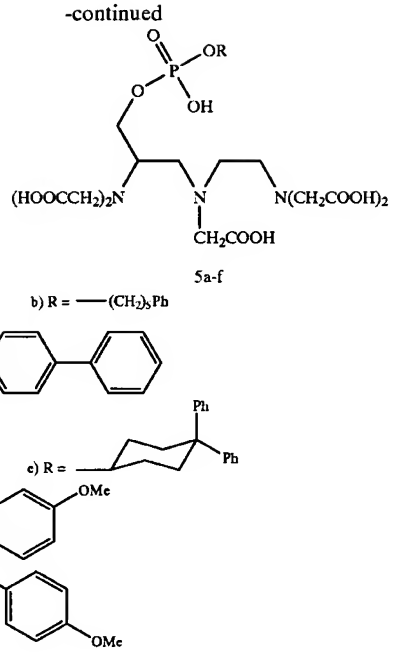


Example 1

Preparation of MS-315-(2)→(3a)→(4a)→(5a)

A. n-Octyloxy Phosphate (3a)

Prepared from a crude phosphoramidite intermediate (2) (prepared from 4.40 g, 6.40 mmol of 1-hydroxymethyl-DTPA-penta-t-butyl ester (1)) by the same procedure described for (3d) and purified by silica gel column chromatography ($CHCl_3$/MeOH) [2.71 g, 44.7% total yield from (2)]. Rf ($CHCl_3$:MeOH=10:1) 0.33.

B. n-Octyl Phospho Diester (4a)

Prepared from the phosphate (3a) (2.70 g, 2.84 mmol) by the same procedure described for (4e) (2.17 g, 85.1%).

C. MS-315 (5a)

The solution of (4a) (2.16 g, 2.41 mmol) in trifluoroacetic acid (20 ml) standing at room temperature for 1 hour. The solvent was evaporated and the residue was dissolved with 5 ml of H_2O. The solution was purified with C_{18} reverse phase silica gel column (Sep-Pak pre-packed cartridge, Waters) (H_2O only —CH_3CN:H_2O=1:4) to give the pure product (5a)(1.13 g, 76.2%). ^{31}P-NMR (D_2O) d2.3.

Example 2

Preparation of MS-317-(2)→(3b)→(4b)→(5b)

A. 5-Phenyl-1-pentyloxy Phosphate (3b)

Prepared from a crude phosphoramidite intermediate (2) (prepared from 2.72 g, 3.96 mmol of 1-hydroxy-DTPA-penta-t-butyl ester (1)) by the same procedure described for (3d) except that the crude product (3b) was used for the next reaction without silica gel column chromatography (4.28 g crude). Rf ($CHCl_3$:MeOH=10:1) 0.26.

B. 5-Phenyl-1-pentyl Phosphodiester (4b)

Prepared from the phosphate (3b) by the same procedure described for (4e) except that the crude product was purified with Sephadex LH 20 chromatography (2.72 g crude). Rf ($CHCl_3$:MeOH=10:1) 0.11.

C. MS-317 (5b)

Prepared from the crude (4b) (2.72 g) by the same procedure described for (5a) [1.12 g, 43.5% total yield from phosphoramidite intermediate (2)]. ^{31}P-NMR (D_2O) d0.1.

Example 3

Preparation of MS-322-(2)→(3c)→(4c)→(5c

A. 2-(4-Biphenylyl)-1-ethoxy Phosphate (3c)

Prepared from a purified phosphoramidate intermediate (2) (3.50 g, 3.87 mmol) by the same procedure described for (3d) except that the crude product of (3c) (4.13 g crude) was used for the next reaction without silica gel column chromatography.

B. 2-(4-Biphenylyl)-1-ethyl Phosphodiester (4c)

Prepared from the phosphate (3c) (4.13 g crude) by the same procedure described for (4e) except that the crude product was purified with Sephadex LH 20 chromatography (2.34 g crude).

C. MS-322 (5c)

Prepared from the crude (4c) (2.34 g) by the same procedure described for (5a) [1.15 g, 43.5% total yield from phosphoramdite intermediate (2)]. ^{31}P-NMR (D_2O) d3.7.

Example 4

Preparation of MS-323-(2)→(3d)→(4d)→(5d)

A. 10-Phenyl-1-decanoxy Phosphate (3d)

To a purified phosphoramidiate (2) (15.20 g, 16.81 mmol) in dist. CH_3CN (50 ml) was added 10-phenyl-1-decanol (9.00 g, 38.39 mmol) and 1H-tetrazole (2.36 g, 33.70 mmol) in dist CH_3CN (50 ml). T-butylhydroperoxide (90%, 2.33 ml, 21.00 mmol) was added and reacted and left for 1 hour at room temperature. The solvent was concentrated in vacuo (ca. 10 ml) and the residue was portioned between AcOEt and H_2O. The organic layer was washed with H_2O and NaCl (sat.), dried lover $MgSO_4$ and evaporated. The residue was purified with silica gel column chromatography (hexanes only—hexanes:ether=1:1 and then $CHCl_3$:MeOH=100:1–50:1) to give the product (3d) (14.12 g, 79.7%) Rf ($CHCl_3$:MeOH=10:1) 0.35.

B. 10-Phenyl-1-decanyl Phosphodiester (4d)

Prepared from the phosphate (3d) (12.27 g, 11.65 mmol) by the same procedure for (4e) (10.52 g, 25 90.3%). Rf ($CHCl_3$:MeOH=10:1) 0.15.

C. MS-323 (5d)

The mixture of (4d) (10.50 g, 10.50 mmol) in cHCl (trace metal grade, 15 ml) and ether (15 ml) was stirred at room temperature overnight and ether was evaporated in vacuo. To the resulting aqueous layer (PH<0) was added cNHOH to adjust the PH to 1.5. The precipitated white solid was collected by filtration and washed with dil. HCl soln. (PH 1.5, 3 times, 100 ml each) and ether (3 times, 200 ml each). The white solid was dried under pump for 24 hours at room temperature to afford pure product (5d) (6.80 g, 90.0%). ^{31}P-NMR (D_2O+NaOD, PH=13.5) d4.9.

Example 5

Preparation of MS-325-(2)→(3e)→(4e)→(5e)

A. 4,4-Diphenylcyclohexyloxy Phosphate (3e)

Prepared from a purified phosphoramidite intermediate (2) (4.52 g, 5.00 mmol) by the same procedure described for (3d) except that silicagel column chromatography solvents (CH_2Cl_2 only—CH_2Cl_2:MeOH=100:1) (2.97 g, 55.4%). Rf ($CHCl_3$:MeOH=10:1) 0.47.

B. 4,4-Diphenylcyclohexyl Phosphodiester (4e)

The solution of (3e) (2.14 g, 2.00 mmol) in 2 M NH_3-MeOH (30 ml) was stirred at room temperature for 5 hours. The solvent was evaporated and the residue (4e) (2.00 g, 98.3%) was used for the next reaction without further purification. Rf ($CHCl_3$:MeOH=10:1) 0.12.

C. MS-325 (5e)

The mixture of (4b) (2.00 g, 1.96 mmol) in cHCl (trace metal grade, 5 ml) and ether (5 ml) was stirred at room temperature overnight. The solvents were evaporated off and the residue was triturated with H_2O (100 ml). The resulting precipitate was filtered and washed with H_2O (5 times, 10 ml each) and ether (5 times, 50 ml each). The solid product was dried under pump at room temperature for 24 hours to give the pure product (5b) (1.18 g, 81.5%). 31P-NMR (D_2O+NaOD, PH=13.5) d–0.3.

Example 6

Preparation of MS-328-(2)→(3f)→(4f)→(5f)

A. 4,4-bis(4-Methoxyphenyl)pentyl Phosphate (3f)

Prepared from 32.5 g (36 mmol) of the crude phosphoramidite (2) and 4,4-bis(4-Methoxyphenyl)pentanol (21.06 g, 70 mmol) by the procedure described for (3d). Chromatography was performed in 50% EtOAc/hexane to yield 18.27 g of a yellow oil which was heavily contaminated with the starting alcohol. Rf (50% EtOAc/Hex) 0.4.

B. 4,4-bis (4-Methoxyphenyl)pentyl Phosphodiester (4f)

A solution of (3f) (18.27 g) was prepared by the same procedure described for (4e) (17.26 g).

C. MS-328 (5f)

Prepared from (4f) (17.26 g) by the procedure described for (5a) yielding 4.88 g of white solid (4.87 mmol, 13% yield from phosphoramidite). ^{31}P-NMR (D_2O) d2.3.

Example 7

In situ Formulation of the N-methyl-D-glucamine Salt of the Gadolinium Complex of 5a (MS-315) (200 mM, 5 mL)

Gadolinium oxide (Gd_2O_3) (0.181 g, 0.5 mmol), compound (5a) (92% by weight, 0.703 g, 1.05 mmol) and N-methyl-glucamine (NMG) (4.1 g, 3.6 mmol) were weighed in a test tube. Deionized water (3.5 mL) was added and the mixture stirred at 95° C. for 7 hours, after which the solution was cooled to room temperature and the volume adjusted to 5.0 mL with deionized water. The solution was filtered through a 2 micron filter to give an aqueous solution of the titled compound.

Example 8

In situ Formulation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5b (MS-317) (200 mM, 4 mL)

Gadolinium oxide (Gd_2O_3) (0.145 g, 0.4 mmol), compound (5b) (81% by weight, 0.706 g, 0.84 mmol) and N-methyl-glucamine (NMG) (0.60 g, 8.1 mmol) were weighed in a test tube. Deionized water (3 mL) was added and the mixture stirred at 95° C. for 6 hours, after which the solution was cooled to room temperature and the volume adjusted to 4.0 mL with deionized water. The solution was filtered through a 2 micron filter to give an aqueous solution of the titled compound.

Example 9

In situ Formulation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5c (MS-322) (200 mM, 4 mL)

Gadolinium oxide (Gd_2O_3) (0.145 g, 0.4 mmol), compound (5c) (79% by weight, 0.729 g, 0.84 mmol) and N-methyl-glucamine (NMG) (0.61 g, 3.1 mmol) were weighed in a test tube. Deionized water (3 mL) was added and the mixture stirred at 95° C. for 6 hours, after which the solution was cooled to room temperature and the volume adjusted to 4.0 mL with deionized water. The solution was filtered through a 2 micron filter to give an aqueous solution of the titled compound.

Example 10

In situ Formulation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5e (MS-325) (200 mM, 5 mL)

Gadolinium oxide (Gd_2O_3) (0.181 g, 0.5 mmol), compound (5e) (95% by weight, 0.820 g, 1.05 mmol) and N-methyl-glucamine (NMG) (0.68 g, 3.5 mmol) were weighed in a test tube. Deionized water (3.5 mL) was added and the mixture stirred at 95° C. for 6 hours, after which the solution was cooled to room temperature and the volume adjusted to 5.0 mL with deionized water. The solution was filtered through a 2 micron filter to give an aqueous solution of the titled compound.

Example 11

In situ Formulation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5f (MS-328) (200 mM, 5 mL)

Gadolinium oxide (Gd_2O_3) (0.181 g, 0.5 mmol), compound (5e) (97% by weight, 0.850 g, 1.05 mmol) and N-methyl-glucamine (NMG) (0.62 g, 3.2 mmol) were weighed in a test tube. Deionized water (3.5 mL) was added and the mixture stirred at 95° C. for 6 hours, after which the solution was cooled to room temperature and the volume adjusted to 5.0 mL with deionized water. The solution was filtered through a 2 micron filter to give an aqueous solution of the titled compound.

Example 12

Preparation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5b (MS-317)

Gadolinium oxide (Gd_2O_3) (0.50 g, 1.38 mmol), compound (5b) (87% by weight, 1.87 g, 2.5 mmol) and N-methyl-glucamine (NMG) (1.53 g, 7.8 mmol) were weighed in a test tube. Deionized water (8 mL) was added then the mixture was stirred at 95° C. for 6 hours, after which the solution was cooled to room temperature and the volume adjusted to 9.0 mL with deionized water. The solution was loaded on a 10-g Sep-Pak® column and eluted with water. Solvent was evaporated under reduced pressure, and the solid, white, glassy residue was dried in high vacuo for 48 hours. Yield: 3.50 g (2.48 mmol, 99%). Anal. Calcd. for $(NMGH^+)_3[Gd(5e^{5-})(H_2O]$ ($C_{47}H_{91}GdN_6O_{30}P$): C, 40.08; H, 6.51; N, 5.97; Gd, 11.16.

Found: C, 40.24; H, 6.69; N, 5.88; Gd; 10.11.

Example 13

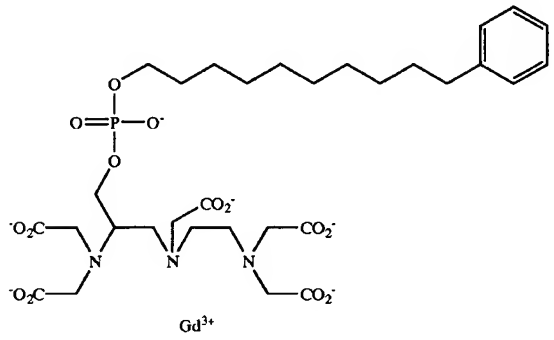
Preparation of the N-methyl-glucamine Salt of the Gadolinium Complex of 5d (MS-323)

Gadolinium chloride hexahydrate ($GdCl_3.6H_2O$) (2.11 g, 5.68 mmol), compound 5d (74% by weight, 5.82 g, 5.98 mmol) and N-methyl-glucamine,(NMG) (6.06 g, 31 mmol) were weighed in a 50-mL round bottom flask. Deionized water (16 mL) was added then the mixture was stirred at 95° C. for 4 hours, and cooled to room temperature. The solution was loaded on a C-18 column (200 g) and eluted with water-methanol 1:1 mixture. Solvent was evaporated under reduced pressure to give a white, glassy solid. Yield: 8.0 g (5.41 mmol, 95%). Anal. Calcd. for $(NMGH^+)$ $3[Gd(5d^{5-})(H_2O]$ ($C_{52}H_{100}GdN_6O_{30}P$): C, 42.27; H, 6.82; N, 5.69; Gd, 10.64. Found: C, 42.04; H, 7.03; N, 5.83; Gd, 9.55.

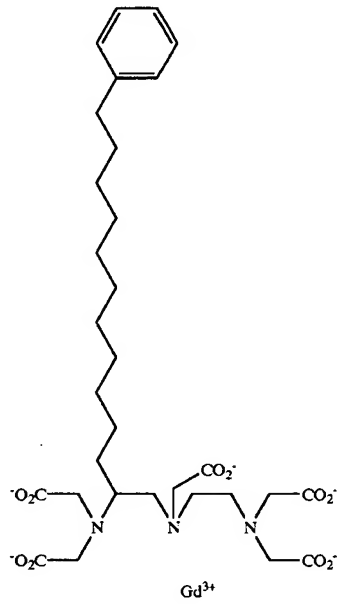
Example 14

The following contrast agent has a binding to HSA of over 95%.

MS-323

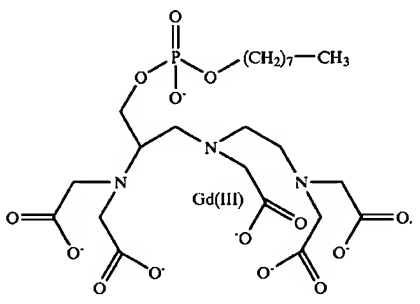


It is shown to have an AUC-conc. (for 0 to 10 minutes) 100% or more greater than that of the following analogue:

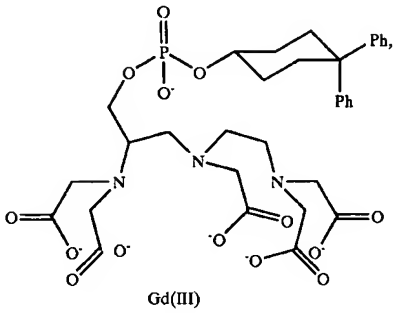


We claim:

1. A diagnostic imaging contrast agent having the following structure:

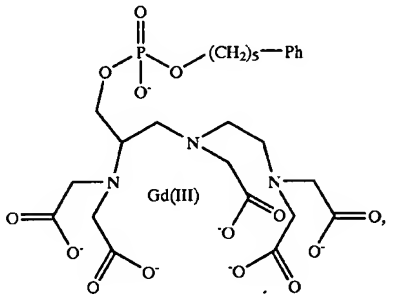


2. A diagnostic imaging contrast agent having the following structure:



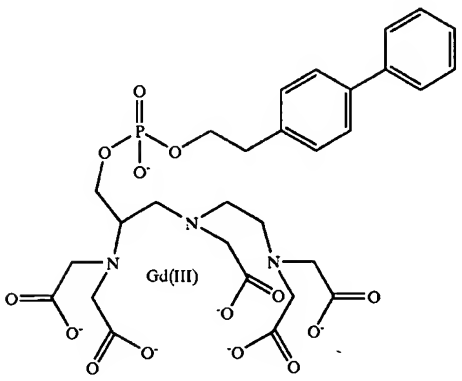
wherein Ph=phenyl.

3. A diagnostic imaging contrast agent having the following structure:

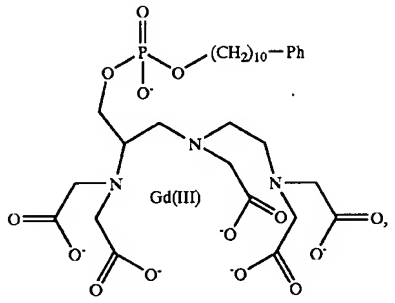


wherein Ph=phenyl.

4. A diagnostic imaging contrast agent having the following structure:

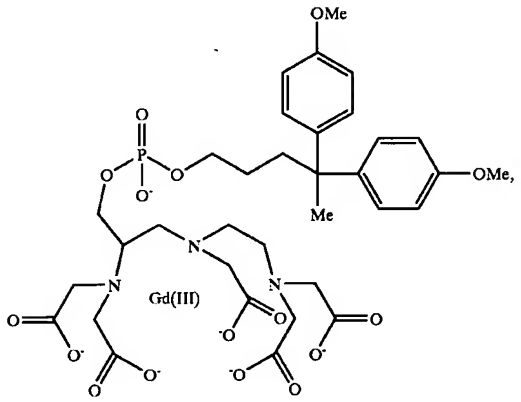


5. A diagnostic imaging contrast agent having the following structure:



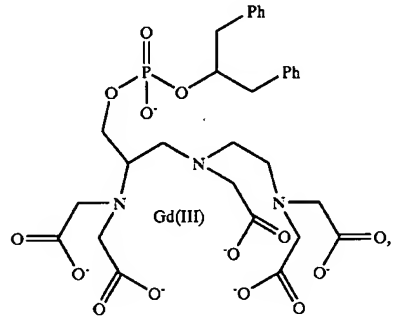
wherein Ph=phenyl.

6. A diagnostic imaging contrast agent having the following structure:



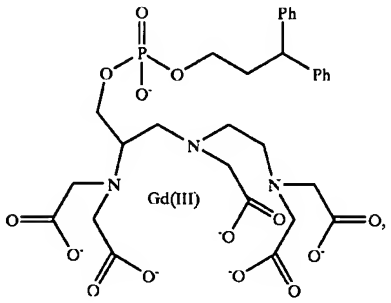
wherein Me=methyl.

7. A diagnostic imaging contrast agent having the following structure:



wherein Ph=phenyl.-

8. A diagnostic imaging contrast agent having the following structure:



wherein Ph=phenyl.

9. A pharmaceutical composition comprising a diagnostic imaging contrast agent according to any of claims 1–8 and a carrier, adjuvant, or vehicle.

10. The pharmaceutical composition according to claim 9, further comprising a free organic ligand or a pharmaceutically acceptable salt thereof.

* * * * *

APPENDIX III

Certificate of Correction and

Maintenance Fee Statement

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,676,929 B2
DATED : January 13, 2004
INVENTOR(S) : Thomas J. McMurry et al.

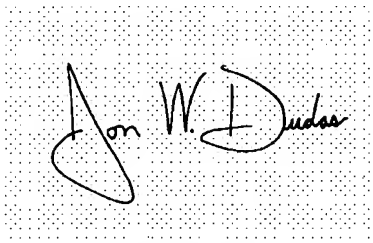
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page,
Item [56], **References Cited**, FOREIGN PATENT DOCUMENTS, please delete "EP 0259358" and insert -- EP 0250358 -- therefor;
Item [74], *Attorney, Agent, or Firm*, after "Richardson", please insert -- , --; and after "P.C.", please insert -- , --;

Column 36,
Line 2, after "8", please insert -- , --.

Signed and Sealed this

Ninth Day of August, 2005



JON W. DUDAS
Director of the United States Patent and Trademark Office

USPTO

Patent Maintenance Fees			01/08/2009 11:25 AM EST
Patent Number:	6676929	Application Number:	10034522
Issue Date:	01/13/2004	Filing Date:	12/20/2001
Window Opens:	01/13/2011	Surcharge Date:	07/14/2011
Window Closes:	01/13/2012	Payment Year:	
Entity Status:	LARGE		
Customer Number:	000000		
Street Address:	FISH & RICHARDSON P.C.		
City:	MINNEAPOLIS		
State:	MN		
Zip Code:	554401022		
Phone Number:	(612) 335-5070		
Currently there are no fees due.			

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APPENDIX IV

Description of Activities During Regulatory Review Period

EPIX Pharmaceuticals, Inc
VASOVIST® MS-325; IND No. 51,172
Submission Index

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1996	**July 19**	**000**	Patricia Love-FDA	Susan Flint-Metasyn (EPIX)	Initial submission of IND # 51,172 MS-325
1997	**January 24**	**001**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Final Reports of the Intravenous Toxicity in Rats; 01/23/97, Rabbits;01-23-1997, Final Pilot Report of Intravenous Dosage-Range Developmental Toxicity study in Rabbits;01/23/1997. ***On February 5, 1997 an amendment was sent due to a typographical error found on page 2 of the cover letter (January 24, 1997, Serial No. 001) on page 2 of the cover letter and page 192 of the submission, this submission contains all corrections***
	February 10	**002**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Results of Phase I Studies. New Phase II Protocols: MS-325-01C, MS-325-03, results of MS-325-01A and 01B
	April 4	**003**	Patricia Love-FDA	Susan Flint-EIX	Protocol Amendment; Change in Protocol: Revision of MS-325-01C & CRFs
	April 10	**004**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Revision of MS-325-02 & CRFs
	April 23	**005**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Addition of clinically significant Adverse Events to protocol MS-325-01C
	July 9	**006**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol-MS-325-04 (Cardiology)
	July 10	**007**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Chemistry- Updated Stability Data-MS-325-20-R (3 lots), MS-325-16-R(4lots), MS-325-DP1(3 lots)

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1997	July 30	008	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-revision of Protocol MS-325-01C Amendment No. 002 & 003
	August 25	009	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- Protocol MS-325-05 (Breast Indication)
	September 22	010	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Addition of 0.125mmol/kg Dosage to Protocol MS-325-01C
	November 3	011	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-Revisions to Protocol MS-325-02: the addition of a microalbumin analysis performed on the first urine specimen of the day
	December 29	012	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigator-MS-325-02 (Malden & Ho), MS-325-04 (Hu), MS-325-05(Hulka & Harms)
	December 29	013	Patricia Love-FDA	Susan Flint-EPIX	Annual Report: December 29, 1996 through December 29, 1997
	December 30	014	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol-Protocol MS-325-02 Blinded Read Protocol and Case Report Forms
1998	February 6	015	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment/Information Amendment: Change in Protocol, Chemistry/Microbiology, Clinical-Complete Report for MS-325-01C, Revision 3 Investigational Drug Brochure, Updated Pharmacokinetic & Adverse event information (all Phase I studies) Revision I of Protocol MS-325-04, revised product Stability Protocol

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1998	**April 28**	**016**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- Two New Investigators: D'Augustino & Esserman
	June 15	**017**	Patricia Love-FDA	Susan Flint-EPIX	Response to Division's Faxed Question's and Comments(05/14/1998) with regard to MS-325-02(SN011;November 3, 1997) and to the Annual Report (SN013; December 29, 1997)
	July 6	**018**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Clinical- 2 Final Clinical Trial Reports : MS-325-01A & MS-325-01B
	August 7	**019**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Pharmacology/Toxicology-4 Revised Toxicity studies (Study No.'s: 96-1403, 95-3288, 1413-001, 1413-002)
	September 21	**020**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Clinical-Final Integrated Clinical/PK Report for MS-325-01C & Updated Investigational Drug Brochure version 3.5
	September 25	**021**	Patricia Love-FDA	Susan Flint-EPIX	Annual Report: for period July 25, 1997 through July 25, 1998
	December 14	**022**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Pharmacology/Toxicology-Study Report for Study # 97-2558
	December 17	**023**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence; Formal Meeting Request for End-of-Phase II

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1998	**December 21**	**024**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Pharmacology/ Toxicology, Clinical- Final Report MS-325-02, Request for Priority Review, Investigational Drug Brochure, Draft Clinical Protocol and Draft CRF 1235-98-546, Draft Clinical Study Protocol and Draft CRF 123-98-576, Pharmacology Study Report #180
	December 23	**025**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Chemistry, Manufacturing, and Control- Changes in the Manufacture of AngioMARK™ (MS-325-20, MS-325-16-R and MS-325 Drug Product)
1999	**January 28**	**026**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Request for CMC Teleconference
	January 28	**027**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence-Pre-Meeting package EOP II Meeting (March 3, 1999)
	February 5	**028**	Paticia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-MS-325-04A and MS-325-05
	February 12	**029**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- Draft Clinical Study, No. 900-414 for AngioMARK
	February 26	**030**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Pre-Meeting Package for the Chemistry, Manufacturing, and Control Meeting (March 3, 1999)
	March 10	**031**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Minutes from EOP II meeting held on March 3, 1999 between EPIX Medical, Mallinckrodt and the FDA.
	March 11	**032**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators for: MS-325-04, MS-325-05

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1999	**March 12**	**033**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocols- MS-325-06 & MS-325-07
	April 8	**034**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: EPIX meeting minutes from End of Phase II CMC Meeting (March 30, 1999),copy of Meeting package(presented at the March 30, 1999 meeting) and revised Stability Matrix design.
	April 15	**035**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocol MS-325-08 (900-414)
	May 7	**036**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- 2 Study Protocols; MS-325-09 and 1235-98-546. Also an updated Investigational Drug Brochure Version 5.
	May 10	**037**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Phase III;EPIX gives Permissions for Robert Wolfangel (Dir of Regulatory Affairs, Mallinckrodt Inc.,) to call the FDA in regards to the Phase 3 clinical trial of AngioMARK
	June 7	**038**	Patricia Love-FDA	Susan Flint-EPIX	EPIX Response to FDA Comments and Questions (FDA Fax May 6, 1999), regarding New Protocol No.MS-325-08(900-414) for AngioMARK (Serial No. 029; 02/12/1999) and Protocol Amendment: New Investigators Protocol No. MS-325-08 (900-414) (Serial No. 035; April 15, 1999)

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1999	**June 15**	**039**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocols; MS-325-09, 1235-98-546 and MS-325-05
	June 22	**040**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Mallinckrodt Inc. to assume the leadership role for Phase 3 clinical Trials with AngioMARK, (due in part that EPIX and Mallinckrodt has formed an alliance) Mallinckrodt will file a separate IND. EPIX gives FDA permission to cross-reference IND #51,172 as necessary to support Mallinckrodt's IND for AngioMARK.
	June 29	**041**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Changes to protocol No. 900-414. These changes reflect the responses to the Division's faxes dated May 6, 1999 and June 11, 1999 containing comments and questions.
	July 12	**042**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For MS-325-04, MS-325-05, MS-325-08 (900-414), MS-325-09, 1235-98-546
	August 13	**043**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocols; MS-325-09 and 1235-98-546
	August 31	**044**	Patricia Love-FDA	Susan Flint-EPIX	EPIX response to Division's Fax of June 11, 1999 containing questions and comments regarding Serial No. 028.
	September 15	**045**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- for Protocols; MS-325-05, MS-325-09, 1235-98-546

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1999	**October 15**	**046**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- for Protocols; MS-325-04, MS-325-09, 1235-98-546
	October 26	**047**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: Revised Clinical Protocol MS-325-06 Clinical Comments and questions (analyzation of ECG data, Exclusion Criteria, Cardiologist ECG Evaluation) with regard to Serial No. 033 Protocols MS-325-06 & MS-325-07
	October 28	**048**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: EPIX Response to Division's Clinical & Statistical Comments (Fax of September 7, 1999) regarding SN036 (May 7, 1999); New Protocols MS-325-09 & 1235-98-546
	October 29	**049**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: EPIX Response to Division's Medical Comments regarding SN 041(Protocol amendment made to Protocol No. 900-414 reflecting the response to the Division's faxes dated May 6, 1999 and June 11, 1999 that contained comments and questions)
	November 5	**050**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in protocol-Changes to Clinical Study Protocol No. MS-325-09 (SN036 May 7, 1999)

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1999	**November 8**	**051**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, for Patient # J-M/003 enrolled in Clinical Study Protocol No. 1235-98-546
	November 11	**052**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 7-Day, Patient # W-H/01 enrolled in Clinical Study Protocol No. MS-325-09
	November 12	**053**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Patient # JJF/01-017 enrolled in Clinical Study Protocol No. MS-325-09
	November 15	**054**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocols MS-325-09 & 1235-98-546
	December 3	**055**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Patient # DHB/01-109 enrolled in Clinical Study Protocol No. MS-325-09. This SAE 1999-04, was an unscheduled surgical repair of a pre-existing aneurysm
	December 10	**056**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Patient # MRH/20-012 enrolled in Clinical Study Protocol No. 1235-98-546
	December 10	**057**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Follow up to Patient # MRH/20-012 enrolled in Clinical Study Protocol No. 1235-98-546
	December 15	**058**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-For Protocol No.s MS-325-06 & 1235-98-546
	December 15	**059**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Synopsis of Protocol No. MS-325-09

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
1999	**December 17**	**060**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Annual Report for the period of July 25, 1998 Thru July 25, 1999
	December 29	**061**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- A Summary of revisions made to the protocol, the revised protocol, and the corresponding case report forms for MS-325-09
	December 29	**062**	Patricia Love-FDA	Susan Flint-EPIX	Updated Investigational Drug Brochure(IDB) version 6.0
2000	**January 14**	**063**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendments: New Investigators-Protocol 1235-98-546
	January 14	**064**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Summary of Conversation regarding Phase 2 protocol MS-325-09 discussion on January 6, 2000
	January 19	**065**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Clarification of Clinical Study Protocol MS-325-09 previously submitted SN061
	February 7	**066**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-Summary of revisions to Protocol MS-325-07
	February 14	**067**	Patricia Love-FDA	Susan Flint-EPIX	Summary and clarification of the ECG monitoring that is being performed in Clinical Study Protocols; MS-325-06, MS-325-07, 1235-98-546 and MS-325-09
	February 15	**068**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Study Protocol No's; MS-325-05, 1235-8-546
	February 28	**069**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day: Patient # J-H/04-003 enrolled in Clinical Study Protocol No. 1235-98-546

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2000	March 2	070	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: End of Phase II Meeting Minutes Request-EPIX requests a copy of Meeting Minutes generated by FDA for the meeting of March 3, 1999
	March 16	071	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- for Protocols: MS-325-05, MS-325-07, 1235-98-546
	April 19	072	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-Protocol MS-325-09
	April 21	073	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 7-Day, Patient # GAJ/014-004 enrolled in Clinical Study Protocol No. MS-325-09
	April 26	074	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment-Change in Protocol- A Summary of revisions to Protocol MS-325-07
	May 12	075	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-Revisions to MS-325-09 to further clarify the masked read process.
	May 15	076	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- Protocols MS-325-04, MS-325-06, MS-325-09
	May 18	077	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 7-Day, Follow-Up, Patient # GAJ/014-004 enrolled in Clinical Study Protocol No. MS-325-09
	May 19	078	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol-Summary of revisions to Protocol 1235-98-546
	May 26	079	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Patient # MCJ/09-006 enrolled in Clinical Study Protocol No. MS-325-09

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2000	June 15	080	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendments: New Investigators-for 3 Study Protocols; MS-325-04, MS-325-09, 1235-98-546
	July 3	081	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Corrected Manufacturer's Report No's corresponding to the Safety Reports submitted year to date.
	July 3	082	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence:EPIX Medical, Inc., Schering AG and Mallinckrodt have formed a strategic alliance for the development, manufacturing and marketing of the MRI for MS-325, under this new alliance the contrast name will revert back to MS-325 from AngioMARK™
	July 12	083	Patricia Love-FDA	Susan Flint-EPIX	A list of changes made to protocol MS-325-08 as well as the changed contrast agent name from AngioMARK™ to MS-325
	July 13	084	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol-Clinical Study Protocol MS-325-11
	July 14	085	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- for 5 Study Protocols; MS-325-07, MS-325-08, MS-325-09, MS-325-11, 1235-98-546
	July 27	086	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol No.- The previously submitted Mallinckrodt Protocol No. 123-98-546 is now being submitted as EPIX Protocol No. MS-325-12
	July 28	087	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol-MS-325-10

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2000	**August 4**	**088**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- A summary of revisions made to protocol MS-325-04 (Images previously submitted, SN015) and the corresponding CRF's
	August 8	**089**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report: 15-Day, Follow-Up Patient # MCJ/09-006 enrolled in Clinical Study Protocol No. MS-325-09
	August 9	**090**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in New Protocol-Summary of revisions to protocol MS-325-09 and the corresponding CRFs
	August 11	**091**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change to Protocol-Changes made to Protocol MS-325-07
	August 14	**092**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-For Protocol No. MS-325-09 and MS-325-12
	August 25	**093**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- For Clinical Study Protocol MS-325-04
	September 11	**094**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: EPIX requesting clarification on a few points pertaining to the revised Phase 3 protocol
	September 14	**095**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Response to the FDA Request for Information- An annotated Version of the revised Clinical Study Protocol No. 1235-98-546
	September 15	**096**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- for MS-325-09 and MS-325-12

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2000	**September 25**	**097**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: EPIX Teleconference Request- Division to hold an internal meeting to discuss EPIX Clinical Program on 10/03/2000 Epix is requesting a teleconference to be scheduled shortly after the internal meeting.
	October 2	**098**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: EPIX attendee list for October 4, 2000 Teleconference with Division to discuss the phase 3 protocol
	October 12	**099**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Pharmacology/Toxicology- Final Study Reports: Study No's. 6622-102, 6622-103, 123-001, RTAW-101, 7L358, 7L359
	October 16	**100**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For MS-325-09 & MS-325-12
	October 26	**101**	Patricia Love-FDA	Susan Flint-EPIX	EPIX response to Division's fax of 7/21/2000 containing statistical and clinical comments regarding SN075, also enclosed is revised MS-325-09.1 and phase 2 MS-325-09
	October 27	**102**	Patricia Love-FDA	Susan Flint-EPIX	EPIX Meeting Minutes from the 10/11/2000 teleconference discussing the Phase 3 Clinical program.
	November 15	**103**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Study Protocols: MS-325-07, MS-325-09, MS-325-12

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2000	**December 18**	**104**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Study Protocols: MS-325-07, MS-325-09, MS-325-10, MS-325-12
	December 21	**105**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- A summary of revisions to Protocol No. MS-325-12
	December 29	**106**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol MS-325-08
2001	**January 16**	**107**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-For Study Protocol MS-325-12
	January 31	**108**	Patricia Love-FDA	Susan Flint-EPIX	Annual Report: Reporting period of 07/25/1999-07/25/2000
	February 12	**109**	Patricia Love-FDA	Susan Flint-EPIX	Response to request for Information: Resulting from meeting minutes from the teleconference held on 10/11/2000 regarding the Phase III Clinical Program
	February 13	**110**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: EPIX requests feedback from Division on the MR equipment imaging parameters with regard to the clinical program
	February 15	**111**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-For Study Protocol MS-325-12
	March 15	**112**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-Study protocol MS-325-12

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2001	**April 6**	**113**	Patricia Love-FDA	Susan Flint-EPIX	Per Divisions Request; A listing of both completed pharmacokinetic studies(MS-325-01A) as well as 2 Pharmacokinetic studies currently in progress(MS-325-06 & MS-325-07)
	April 6	**114**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Additional clarification regarding study # 6622-103 previously submitted on 10-10-2000 (SN099) and to the incorrect labeling
	April 6	**115**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: EPIX response- Clinical & Statistical Comments regarding SN095
	April 6	**116**	Patricia Love-FDA	Susan Flint-EPIX	Response to FDA Request for Information: EPIX response to Division's fax regarding the dilution of MS-325. Also included is the narrative of the Dosing Regimen
	April 12	**117**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Confirmation that EPIX will be performing the MRA blinded read protocol for the Phase 3 study with regard to clinical study protocol MS-325-12
	April 13	**118**	Patricia Love-FDA	Susan Flint-EPIX	EPIX response to Division's fax of 02/20/01 containing Statistical Comments and to the Division's fax of 04/04/01 containing clinical comments also included are changes to Clinical Study Protocol MS-325-12
	April 17	**119**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators-for Protocols MS-325-07 & MS-325-12

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2001	April 20	120	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Changes made to Protocol No. MS-327-07
	May 17	121	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators for MS-325-12
	June 5	122	Patricia Love-FDA	Susan Flint-EPIX	Response to Division's fax dated 05/23/2001: containing clinical comments with regard to SN 106
	June 12	123	Patricia Love-FDA	Susan Flint-EPIX	Response to Division's Fax dated 05/23/2001:with regard to clinical comments of serial No. 117 and 118
	June 14	124	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol-MS-325-13; addresses the issue mentioned in the Division's fax of December 27, 2000, to incorporate a greater number of vascular beds
	June 18	125	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators for Protocol No. MS-325-12
	June 19	126	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Listing of all personnel (and their respective CV's) that will be involved in the blinded read for phase 3 Protocol No. MS-325-12(submitted on 4/13/2001: SN118)
	July 3	127	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Clinical- The Executive Summary for End of Phase 2 report for protocol MS-325-09. Also EPIX requests a meeting with Division for an end of phase 2 meeting
	July 16	128	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- to Protocol MS-325-12

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2001	**July 31**	**129**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Response to FDA Request for Information-EPIX response to division's request of an proposed agenda for the EOP2 meeting scheduled for August 28, 2001, also minor changes to protocol MS-325-13
	August 8	**130**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Response to FDA Request for Information-Responses to Division's fax dated 08/02/2001 pertaining to the microbiology comments for the EOP2 meeting scheduled for 08/28/2001
	August 15	**131**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- An Analytical Study Protocol, also included are the 1572 and CV for the Principal Investigator
	August 17	**132**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: A brief synopsis of key points and listing of key clinical communications between FDA & EPIX in preparation for the meeting on 08/28/2001
	August 21	**133**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence:Copies of the overhead presentation for the End-of-Phase 2 meeting scheduled for 08/28/2001
	August 24	**134**	Paticia Love-FDA	Susan Flint-EPIX	General Correspondence: Resubmitting Slides-an abbreviated number of slides are being resubmitted due to a recent change in the 08/28/2001 meeting-slides are identical to submission SN133(08/21/2001) but are rearranged for presentation convenience

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2001	**September 14**	**135**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigator- For Protocol MS-325-12
	September 20	**136**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Blinded Read- Additions and deletions of readers involved in the read for the Phase 3 protocol #MS-325-12, also included are the CV's and licenses of 2 replacement readers
	September 21	**137**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Meeting Minutes: Clinical Development Program- EPIX meeting minutes from the 08/28/01 teleconference discussion of the Clinical Development Program for MS-325
	October 2	**138**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Response to Request for Information- Divisions Clinical/Statistical Comments (fax dated August 28, 2001) EPIX response to request of Information of all clinical issues with regard to MS-325-13
	October 10	**139**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: In response to the Division's request EPIX has designed 3 prospective studies based on analysis of data obtained in the MS-325-09 phase 2 study: Region of Data, Clinical Blinded read, Analyze ROI Measurements
	October 18	**140**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocol No. MS-325-12 & MS-325-13

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2001	October 24	141	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: EPIX Reponses to Clinical/Pharmacology and Pharmacology/Toxicology comments in the 08/28/2001 Agency Fax, Also EPIX requests the Division's Meeting Minutes of the T-con held on August 28, 2001
	November 6	142	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- An executive summary of both the Clinical & Technical blinded reads of renal artery MRA studies along with reports for both of these studies. These studies address the Division's fax comments of August 31, 2001
	November 15	143	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Study Protocol No.'s; MS-325-13, MS-325-04A
	November 16	144	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Protocol- Data from Study Protocol BR-09-TR-SV (as requested by the Division Fax of August 28, 2001) Also included is Protocol MS-325-15
	December 5	145	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigator- For Protocol MS-325-04 and MS-325-13
	December 27	146	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Phase III Trial Centers- EPIX request Division's input regarding inclusion of Trial Centers previously used for prior studies to be used in new studies

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2002	**January 16**	**147**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocols: MS-325-13, MS-325-14, MS-325-15
	January 25	**148**	Patricia Love-FDA	Susan Flint-EPIX	Response to FDA Request for Information: A Principal Investigator list for protocol MS-325-14, as requested by the Division with regard to Serial No. 146(December 27, 2002)
	January 31	**149**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Protocols; MS-325-04, MS-325-13, MS-325-14
	February 14	**150**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Revised Protocol MS-325-13 Modification of inclusion Criteria
	February 14	**151**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence, Other: EPIX letter asking Division if they would like a draft of the Executive summary for MS-325-12 prior to the data being presented at the American College of Cardiology Annual Meeting on 03/18/2002
	February 25	**152**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- The revised protocol amendment for protocol MS-325-15
	February 28	**153**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Three revised FDA Forms 1572 for MS-325-13, and one new FDA Form 1572 and curriculum vitae for MS-325-14
	March 8	**154**	Patricia Love-FDA	Susan Flint-EPIX	Annual Report: Reporting period of July 25, 2000 thru July 21, 2001
	March 27	**155**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- MS-325-13, MS-325-14, MS-325-15

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2002	**April 16**	**156**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigator- For protocol MS-325-13, MS-325-14, MS-325-15
	April 23	**157**	Patricia Love-FDA	Susan Flint- EPIX	Protocol Amendment: Change in Protocol- Revised Protocol MS-325-07
	April 26	**158**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Change in Protocol- Revised Protocol MS-325-14; change to reflect an update to the MR parameters
	May 2	**159**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Revised Protocol Amendment Summary previously submitted incorrectly (April 23, 2002) with MS-325-07
	May 7	**160**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Environment Claim for Exclusion- Request for Environmental Waiver for NDA Filing
	May 15	**161**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New & Revised form 1572- For protocols MS-325-07, MS- 325-13 and MS-325-14
	June 13	**162**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Form FDA 1572, Revised Form FDA 1572- For MS-325-07, MS-325-13, MS-325-14, MS-325-15
	July 1	**163**	Patricia Love-FDA	Susan Flint-EPIX	Information Amendment: Pharmacology/Toxicology-Final report for study No. RTAW-107
	July 11	**164**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New form FDA 1572, Revised Form FDA 1572- For Protocols MS-325-13, MS-325-14, MS-325-15

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2002	**August 15**	**165**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New & Revised Form FDA 1572- for Protocol MS-325-13
	September 13	**166**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Form FDA 1572 Revised form FDA 1572-Protocols MS-325-13, MS-325-14, MS-325-15
	October 10	**167**	Patricia Love-FDA	Susan Flint-EPIX	IND Safety Report-15-Day, Initial, for Patient # R-M/136-003 enrolled in Clinical Study Protocol No. MS-325-13
	October 15	**168**	Patricia Love-FDA	Susan Flint-EPIX	Response to Request for Information: Qualification of Principal Investigator for renal protocol, MS-325-14
	October 16	**169**	Patricia Love-FDA	Susan Flint-EPIX	New & Revised form FDA 1572-For Study Protocols: MS-325-14 and MS-325-15
	November 18	**170**	Patricia Love-FDA	Susan Flint-EPIX	General Correspondence: Listing of personnel involved with the blinded read for Protocol MS-325-13
	November 19	**171**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New and Revised Form 1572- For Study Protocols; MS-325-14 and MS-325-15
	November 21	**172**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Response to Request for Information, New Protocol-Clinical Study Protocol MS-325-16: Protocol was written in Response to Division's request for Safety & Pharmacokinetic data
	December 17	**173**	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New & Revised Form FDA 1572-For Study Protocols MS-325-14, MS-325-15, MS-325-16

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2003	January 17	174	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: New Investigators- For Study Protocols MS-325-14 & MS-325-15
	February 3	175	Patricia Love-FDA	Susan Flint-EPIX	Annual Report- For Reporting period July 25, 2001 thru July 25, 2002
	February 14	176	Patricia Love-FDA	Susan Flint-EPIX	Protocol Amendment: Revised Form FDA 1572-Protocol Amendments for MS-325-14, MS-325-15,
	March 3	177	Florence Houn-FDA	Debra Suckney-EPIX	Protocol Amendment: New Protocol- MS-325-18. Start date planned for March 17, 2003 after receipt of IRB approval.
	March 6	178	Florence Houn-FDA	Debra Suckney-EPIX	General Correspondence: Abbreviated and Synopses Study Report- EPIX requests Division approval to submit an abbreviated study report for MS-325-04/04a In addition EPIX requests permission to submit synopses study reports for the following protocols: MS-325-05, MS-325-08, MS-325-10 and MS-325-11
	March 11	179	Florence Houn-FDA	Robert Morgan-EPIX	Other: Request for Pre-NDA Meeting meeting to discuss format and content of NDA for MS-325 In addition, EPIX requests guidance regarding several sections of NDA & proposals to expedite review.
	March 14	180	Florence Houn-FDA	Debra Suckney-EPIX	Protocol Amendment: New FDA Form 1572, Revised FDA Form 1572-To protocol MS-325-16 & MS-325-18

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2003	March 18	181	Florence Houn-FDA	Debra Suckney-EPIX	General Correspondence: Change in plans to submit interim reports for mild and moderate cohorts for MS-325-07, EPIX will submit complete study report instead in the NDA submission
	March 26	182	Florence Houn-FDA	Robert Morgan-EPIX	Follow-up letter to previous request for a pre-NDA meeting. EPIX attached a draft version of discussion items, questions, draft meeting goals, draft agenda and a proposed list of attendees
	April 7	183	Florence Houn-FDA	Robert Morgan-EPIX	General Correspondence: Meeting package for Pre-NDA discussion: Meeting goals, agenda, attendees and questions & skeleton of planned eNDA
	April 18	184	James Moore-FDA	Robert Morgan-EPIX	IND Safety Report: 15-Day, Patient No. GMC/002 enrolled in Clinical Study Protocol No. MS-325-18 EPIX notified of Serious Adverse Event on 4/15/2003; follow up report to be provided once additional clinical information is available
	May 2	185	James Moore-FDA	Robert Morgan-EPIX	General Correspondence: EPIX provides Division with additional information with regard to the scheduled May 20, 2003 Pre-NDA meeting
	May 13	186	Florence Houn-FDA	Debra Suckney-EPIX	Protocol Amendment: Revised Protocol for MS-325-18

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2003	May 15	187	James Moore-FDA	Robert Morgan-EPIX	IND Safety Report: 15-Day, Follow-Up, Patient # GMC/002 enrolled in Clinical Study Protocol No. MS-325-18; Patient died of cardiac arrest (primary cause) with septicemia as secondary cause of death. Patient's family refused permission for autopsy. Unlikely related to MS-325
	May 19	188	James Moore-FDA	Debra Suckney-EPIX	General Correspondence: Slides for May 20, 2003 Pre-NDA Meeting- 25 copies
	June 9	189	James Moore-FDA	Debra Suckney-EPIX	General Correspondence, Meeting Minutes: EPIX minutes of the May 20, 2003 Pre-NDA meeting
	June 9	190	James Moore-FDA	Debra Suckney-EPIX	Response to Request for Information: Abbreviated Study Reports- Submitting Sample Final Synopsis for Study Report MS-325-11
	June 30	191	Florence Houn-FDA	Debra Suckney-EPIX	Protocol Amendment: Changes in Protocol-To Clinical Study Protocol No. MS-325-18
	July 23	192	Sally Loewke-FDA	Robert Morgan-EPIX	Requesting meeting w/ FDA based on previous statistics request/comment by FDA to EPIX. In order to best meet FDA request, EPIX requests meeting w/ FDA. Included draft meeting agenda, list of attendees and questions/items for discussion.
	July 31	193	Florence Houn-FDA	Debra Suckney-EPIX	Protocol Amendment: New Investigator-For Protocols MS-325-18, MS-325-05
	September 24	194	Jane Axelrad-FDA	Robert Morgan-EPIX	Other: Request for User Fee Waiver as a small business submitting its first human drug application

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2003	**October 14**	**195**	James Moore-FDA	Debra Suckney-EPIX	EPIX request confirmation from the Division on the correct filing of the eNDA
	November 24	**196**	James Moore-FDA	Debra Suckney-EPIX	IND Safety Report: A modification to the IND Safety Report to patient enrolled in Study MS-325-18 (previously submitted 05/15/2003 Serial No. 187)
2004	**May 13**	**197**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Protocols- MS-325-19 & MS-325-20
	June 22	**198**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators- For MS-325-19 and MS-325-20
	July 15	**199**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Form FDA 1572 For MS-325-19 and MS-325-20
	August 12	**200**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators- 4 New Investigators to MS-325-19
	August 12	**201**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: Change in Protocol- To increase the number of healthy volunteers to be enrolled at site # 202 Protocol No. MS-325-19
	August 25	**202**	George Mills-FDA	Robert Morgan-EPIX	Protocol Amendment: New Protocol- To assess the safety and pharmacokinetics of MS-325(0.01, 0.03, 0.05, or 0.1 mmol/kg) in Japanese Healthy Male Subjects
	September 8	**203**	George Mills-FDA	Debra Feldman-EPIX	General Correspondence: EPIX Name Change; Notification to Division of EPIX name change to EPIX Pharmaceuticals, Inc.
	September 15	**204**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators- For Protocols MS-325-19 & MS-325-20

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2004	October 15	205	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators- For MS-325-19
	November 15	206	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New & Revised forms 1572 for protocol MS-325-19
	December 20	207	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: Revised Form FDA 1572 for MS-325-19
2005	January 5	208	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: Change in Protocol-For MS-325-19- additional sites to be added in Europe due to slow enrollment in U.S. & Other minor editorial changes.
	January 12	209	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators, Revised 1572-For MS-325-19
	January 20	210	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: Site Specific Change- For MS-325-19, an additional 5 patients for site 202
	January 28	211	George Mills-FDA	Debra Feldman-EPIX	Annual Report: For periods of July 25, 2002-August 02, 2004 (57 volumes)
	February 9	212	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigator, Revised 1572- For MS-325-19
	March 17	213	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigators, Revised 1572- For Protocol 305608 (Japanese phase I study in Hawaii)
	April 19	214	George Mills-FDA	Robert Morgan-EPIX	Protocol Amendment: Revised Protocol-Revised Phase I Japanese study 3050608 to include Females

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2005	**April 22**	**215**	George Mills-FDA	Robert Morgan-EPIX	Protocol Amendment: Change in Protocol- Changes include; reduction in No. of patients, decoupling sites and changing inclusion criteria to revise requirements for CAD pts.
	April 26	**216**	George Mills-FDA	Debra Feldman-EPIX	Information Amendment: Pharmacology/Toxicology- A non-clinical report titled "Inhibitory Effects of ZK 236018 (MS-325) and its Ligand ZK 233284 *In vitro* on Cytochrome P450 Dependent Metabolism of Model Subtrates."
	June 17	**217**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigator-Revised 1572- For Protocol MS-325-20
	July 15	**218**	George Mills-FDA	Debra Feldman-EPIX	Protocol Amendment: New Investigator-Revised 1572-For Protocol MS-325-20
	October 3	**219**	George Mills-FDA	Debra Feldman-EPIX	Annual Report: For reporting period August 2, 2004- June 1, 2005, also contains the updated Investigational Brochure Version 11
2006	**January 27**	**220**	James Moore-FDA	Aarati Sridharan-EPIX	General Correspondence: Change in EPIX Regulatory Contact-Robert Morgan and Debra Feldman are no longer with EPIX, Aarati Sridharan is the main point of contact in the interim for IND 51, 172

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2006	April 13	221	James Moore-FDA	Aarati Sridharan-EPIX	Response to Request for Information: EPIX Response to Division's Request; Currently EPIX has no on-going studies with MS-325, so the IB will not be revised
	October 18	222	George Mills-FDA	Aarati Sridharan-EPIX	Annual Report: For reporting period of June 1, 2005 thru August 1, 2006
2007	February 22	223	James Moore-FDA	Aarati Sridharan-EPIX	Response to Request for Information: Revised IB to remove misleading language per FDA request of March 10, 2006. Also provides Dr. Lederman at NIH permission to reference IND 51,172 for his ISS with MS-325
	June 7	224	R. Dwaine Rieves-FDA	Aarati Sridharan-EPIX	Information Amendment: Chemistry- Minor changes to the manufacturing process. Also included is the certificate of analysis
	October 29	225	R. Dwaine Rieves-FDA	Aarati Sridharan-EPIX	Annual Report: For the reporting period of August 1, 2006 thru August 17, 2007
2008	February 1	226	R. Dwiane Rieves-FDA	Margaret J. Uprichard-EPIX	Response to Request for Information: Blinded re-Read- The re-read protocol of December 21, 2007 & the correction to Statistical Analysis Plan of January 23, 2008 (both previously submitted to the NDA) Division has requested these documents be submitted to the IND

YEAR	DATE	SERIAL No.	TO	FROM	DESCRIPTION
2008	**February 4**	**227**	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Information Amendment: Final Study Reports for MS-325-19, MS-325-20, Phase I Bridging Study 305608
	April 3	**228**	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Other: EPIX Request for Teleconference to Discuss and obtain agreement on the components of the NDA resubmission
	May 1	**229**	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Other: EPIX submits a Type C Meeting background Package for the upcoming June 5, 2008 Teleconference with regard to the NDA Resubmission

VASOVIST IND CORRESPONDENCE LOG

Date	To	From	Description
04/10/1996	Susan Flint, METASYN	Santford Williams, FDA	Fax: Draft comments regarding pre-IND meeting packet
04/16/1996	Susan Flint, METASYN	Dr. Jim Cheever, FDA	Phone: Review contents of fax dated 04/10/1996 regarding pre-IND meeting
06/04/1996	Susan Flint, METASYN	Dr. David Udo, FDA	Phone: Verification of Gd amounts in each proposed dose in protocol
06/15/1996	Santford Williams, FDA	Susan Flint, METASYN	Fax: METASYN agrees to perform the signal saturation study – If the study is not completed prior to IND filing, will complete the study and file report within 2 months of the IND filing date
07/01/1996	Susan Flint, METASYN	Santford Williams, FDA	Phone: Committed to file the signal saturation study in the IND and discussed required number of copies
07/25/1996	Susan Flint, METASYN	Santford Williams, FDA	Receipt of IND #51,172 (Date of Submission - July 19, 1996; Date of Receipt – July 22, 1996)
07/25/1996	Dr. David Place, FDA	Susan Flint, METASYN	Mail: Disks containing CMC sections of MS-325 IND
08/23/1996	Amy Chapman, FDA	Susan Flint, METASYN	Phone: Metasyn to start Phase 1 clinical trial. FDA had meeting to discuss EPIX; IND not on hold but several issues that would be communicated in a few weeks
08/29/1996	Santford Williams, FDA	Susan Flint, METASYN	Phone: Status of draft FDA comments for IND #51,172 - was informed they are in review. Confirmed low to zero impact on protocol field implementation
09/19/1996	Santford Williams, FDA	Susan Flint, METASYN	Phone: Second inquiry on status of draft comments on the IND #51,172
11/06/1996	Santford Williams, FDA	Susan Flint, METASYN	Phone: Questions regarding a combined Phase II/III trial. Issue concerning two different departmental physicians at the same hospital participating in trials. Update of clinical trials; intention to file Radiology first NDA
11/08/1996	Santford Williams, FDA	Susan Flint, METASYN	Phone: Questions from 11/06/1996 will be answered once proposal to IND #51,172 is filed

Date	To	From	Description
11/08/1996	Susan Flint, METASYN	Santford Williams, FDA	Fax: Draft pharmacokinetics comments for IND #51,172
11/25/1996	Susan Flint, METASYN	Santford Williams, FDA	Fax: Draft CMC comments for IND #51,172
01/06/1997	Dr. Patricia Love, FDA	Susan Flint, METASYN	Mail: Name change from Metasyn, Inc. to EPIX Medical, Inc.
01/09/1997	Santford Williams, FDA	Susan Flint, EPIX	Fax: Request for clarification of CMC comments for IND #51,172 included in FDA fax dated 11/25/96
01/09/1997	Dr. Patricia Love, FDA	Susan Flint, EPIX	Mail: Request for meeting to discuss Phase II and Phase IC programs. Overview of IND #51,172 filing intentions (time period, content, plan)
01/10/1997	Susan Kummerer, FDA	Susan Flint, EPIX	Fax: Copy of 01/09/97 meeting request. Request status of the clinical fellowship program.
01/13/1997	Susan Flint, EPIX	Santford Williams, FDA	Fax: Clinical comments pertaining to IND #51,172 Serial #000 dated 07/19/96
01/21/1997	Santford Williams, FDA	Susan Flint, EPIX	Phone: Meeting arranged for 03/12/97; Dr. Botstein's attendance requested
01/27/1997	Susan Flint, EPIX	Santford Williams, FDA	Email: FDA/EPIX meeting scheduled for 03/12/97 at 3pm
02/05/1997	Dr. Patricia Love, FDA	Susan Flint, EPIX	Mail: Revision of Amendment 001 cover letter originally sent 01/24/97; multiple typographical errors corrected
02/12/1997	Dr. Patricia Love, FDA	Susan Flint, EPIX	Mail: IND #51,172 meeting package dated 02/12/97
02/21/1997	Susan Flint, EPIX	Santford Williams, FDA	Fax: IND #51,172 draft pharmacokinetics and microbiology comments dated 07/19/96
02/24/1997	Mallinckrodt (MKG) & EPIX	Susan Flint, EPIX	Email: Conversation with Santford Williams, FDA: Dr. Robert Yaes to be medical reviewer. MKG open phone line request denied. Pre-meeting feedback expected. Meeting scheduled for 03/12/97
02/28/1997	Susan Flint, EPIX	Dr. E. Kent Yucel, EPIX	David Udo, PhD, FDA, pharmacokineticist, telephoned requesting: Data regarding % of albumin binding of MS-325 at 3 dose levels for Phase I, In vitro data – included in IND #51,172

Date	To	From	Description
03/03/1997	Dr. David Udo, FDA	Susan Flint, EPIX	Mail: Copy of Phase 1A trial PK data: pages 645-674 of Amendment No. 002 (submitted to FDA on 02/10/97). Report 130 (submitted in original IND)
03/03/1997	Dr. David Udo, FDA	Susan Flint, EPIX	Fax: Copy of Phase 1A trial PK data: Pgs 661-666 of Amendment No. 002 (submitted to FDA on 02/10/97). Report 130 (submitted in original IND). Confirmation that all documents FedEx'd
03/12/1997	FDA	EPIX	03/12/97 EPIX Medical Presentation to the FDA
03/18/1997	Santford Williams, FDA	Susan Flint, EPIX	Email: Assurance meeting minutes to be sent. Request status of Dr. Yaes' comments
04/18/1997	Santford Williams, FDA	Susan Flint, EPIX	Fax: Clarification of clinically significant Adverse Event criteria
04/22/1997	Anthony Mucci, FDA	Susan Flint, EPIX	Mail: Description of the Cochran-Armitrage test for trends. Selected pages from Ch. 9 of *Statistical Methods for Rates and Proportions*
05/02/1997	Susan Flint, EPIX	Dr. Eric Jones, FDA	Phone: Clarification of Phase IC Protocol - wanted to be reassured that we added clinically significant changes in heart rate and bp to the protocol.
05/05/1997	Santford Williams, FDA	Susan Flint, EPIX	Phone: Inform that Protocol MS-325-01C will commence on May 7
05/09/1997	Santford Williams, FDA	Susan Flint, EPIX	Phone: Inform that MS-325-02 will commence next week. New CSO Phyllis Doulaveris
05/12/1997	Susan Flint, EPIX	Phyllis Doulaveris, FDA	Fax: Medical reviewer's recommendations for Protocols MS-325-01C and MS-325-02
05/15/1997	Dr. Robert Yaes, FDA	Susan Flint, EPIX	Fax: Response to medical reviewer's recommendations and request to discuss
05/20/1997	Dr. Eric Jones, FDA	Susan Flint, EPIX	Fax: Response to items regarding Protocol MS-325-01C
05/20/1997	Dr. Eric Jones, FDA	Susan Flint, EPIX	Fax: Response to items regarding Protocol MS-325-02
07/15/1997	Dr. Patricia Love, FDA	Susan Flint, EPIX	Mail: Correction to Serial #s

Date	To	From	Description
09/17/1997	Dr. Patricia Love, FDA	Susan Flint, EPIX	Mail: Clarification of Adverse Event page in CRF (IND Serial #008)
09/18/1997	Susan Flint, EPIX	FDA	Phone: New medical reviewer: Dr. Padma Rao is working with Dr. Yaes
10/08/1997	Dr. Eric Jones, FDA	Susan Flint, EPIX	Phone: 1. Update on Phase 1C trial 2. Concern regarding renal issue
12/02/1997	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical comments on Protocol MS-325-01C (Sept. 22, 1997 submission)
12/30/1997	Rubynell Jordan, FDA	Susan Flint, EPIX	Fax: Manufacturing process to be modified. Toxicology plan for MS-325
01/05/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: FDA acknowledges receipt of EPIX Annual Report and recognizes safety issue
01/06/1998	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Ruby Jordan (CSO) called on behalf of Dr. Sadrieh to clarify that EPIX is not using the new manufacturing process in the field
01/07/1998	Patricia Y. Love, FDA	Susan Flint, EPIX	Mail: Additional toxicology studies to be added to IND
01/08/1998	Susan Flint, EPIX	Dr. Sadrieh, FDA	Phone: Conversation to see what kind of impurity profile we have in the new process versus the old process
01/09/1998	Dr. Sandrieh, FDA	Susan Flint, EPIX	Phone: Call with agency explaining the Impurity Process Plan
01/15/1998	Rubynell Jordan, FDA	Susan Flint, EPIX	Fax: Conference call request regarding chemistry questions from EPIX & Mallinckrodt
01/20/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Dates that Dr. David Place will be available for a conference call
01/21/1998	Ruby Jordan, FDA	Susan Flint, EPIX	Phone: Confirmed date and time for conference call with FDA
01/27/1998	Beverly L. Slayton, EPIX	Rubynell Jordan, FDA	Phone: FDA questions with regard to IND, free EDTA, manufacturing procedure, and the drug product. Would like to discuss before meeting on 02/06/98
01/27/1998	Patricia Y. Love, FDA	Susan Flint, EPIX	Mail: Information (Impurity Profile) to be added to IND
01/29/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Call cancelled and rescheduled, Brief discussion regarding Dr. Place's concern with GdEDTA amounts

Date	To	From	Description
02/06/1998	Susan Flint, EPIX	Dr. Sadrieh, FDA	Phone: EPIX is still in need of Dr. Sadrieh's input with regards to toxicology plan
05/05/1998	Patricia Y. Love, FDA	Susan Flint, EPIX	Mail: Request permission for Mary Hamilton (Mallinckrodt) to be the contact person for any CMC or Phase III related issues for MS-325
05/14/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical comments and questions for the sponsor (Serial #011 and #013)
12/17/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: End of Phase II submission will be delivered by Dec 22. EPIX requests meeting.
12/23/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Meeting date set for March 2, 1999 1pm. Agency has also requested 9 additional copies of Vol 1.1
12/30/1998	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: The meeting date of March 2, 1999 has been changed. She will call back to confirm a new date of March 4, 1999.
01/06/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Meeting confirmed for 3:30pm Wednesday March 3
01/14/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Ruby Jordan requested CMC questions be forwarded to her to determine whether a meeting or a T-con should be scheduled
02/05/1999	Susan Flint, EPIX	FDA	Phone: CMC Meeting set for March 30, 1999
02/23/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Location of meeting – conference room M on the cafeteria level
03/01/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Biopharmacology/ Pharmacokinetic comments and recommendation with regards to submission #024
03/01/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Pre-Meeting update, regarding March 3, 1999 meeting tentative issues
03/12/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Dates of the relevant submissions with conflicting info regarding percent plasma protein binding of AngioMark
03/17/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: Questions from EPIX regarding FDA's definition of a Truth Panel and CMC meeting

Date	To	From	Description
03/18/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Request for information – questions in preparation for the March 30, 1999 meeting
03/22/1999	Ruby Jordan, FDA	Susan Flint, EPIX	Phone: Bridging Tox Information regarding March 30, 1999 meeting
03/25/1999	Susan Flint, EPIX	Ruby Jordan, FDA	Phone: 3 issues to be discussed at the March 30, 1999 meeting
03/26/1999	Susan Flint, EPIX	Meri Bloom, EPIX	Email: Dr. Nakissa Sadreih will be returning to our division
03/26/1999	Eric Jones, FDA	Susan Flint, EPIX	Phone: EPIX wanted to know what the Agency meant by "truth panel." Eric explained it was most unfortunate for us to have been told these words by the agency and could not give his opinion until he discussed this with Dr. Love.
04/08/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Explanation for when Truth Panel is needed
05/06/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical comments and questions regarding submission #029
05/14/1999	Rubynell Jordan, FDA	Susan Flint, EPIX	Phone: Gary Stevens and Susan Flint request a T-con with Dr. Sobhan
06/11/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Consult to HFD-580 (Division of Reproductive and Urologic Drug Products)
06/11/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical comments regarding submission #028
07/20/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical comments regarding submission #033
09/03/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: "Guidance" on Phase II and II is ready from submission #036. Will fax questions on Tuesday.
09/07/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Clinical and statistical comments regarding submission #036
09/08/1999	Susan Flint, EPIX	Tia Harper-Valazquez on behalf of Rubynell Jordan, FDA	Fax: Comments regarding submission #041
10/21/1999	Rubynell Jordan, FDA	Susan Flint, EPIX	Phone: Several messages left for Rubynell Jordan & R. K. Leedum

Date	To	From	Description
10/21/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Discussion regarding two areas of concern (ECG Monitoring & Placebo Group). Ruby suggests submitting the revised protocol response and await the agencies response
10/27/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Left voicemail that phone call with FDA has been set for 11/9 at 10:30am. Will only occur if FDA receives response to their fax tomorrow – response was sent out.
11/10/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Fax: Comments in response to submission #048 dated October 28, 1999
12/14/1999	Susan Flint, EPIX	Rubynell Jordan, FDA	Phone: Archana Reddy will be the new project manager for the AngioMark IND
01/07/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: T-con minutes from 01/5 - Discussion to clarify issues raised by Dr. Jones in the second paragraph of the November 10, 1999 fax to Susan Flint regarding plans to move forward with the P2 Clinical trials
02/03/2000	Archana Reddy, FDA	Susan Flint, EPIX	Email: EPIX to implement the revised Phase 2 protocol that was sent to the agency on 12/30/99 – beginning our sites on 02/04/00
02/06/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Minutes from the March 3, 1999 industry meeting
02/07/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: As requested, a copy of the teleconference minutes from January 5
02/10/2000	Ms. Bloom, EPIX	Archana Reddy, FDA	Fax: ECG general recommendations for data, Dr. Jones' response to submission #048
02/11/2000	Susan Flint, EPIX	Eric Jones, FDA	Phone: left a VM with questions regarding ECG Monitoring that EPIX is doing in the renally impaired protocol that we filed on 02/07/2000
02/21/2000	Susan Flint, EPIX	Algroup Wheaton – Pharmaceutical & Cosmetic Packaging	Mail: Holder of Drug master file 10095 as amended on 04/01/00 authorizing the FDA to review relevant file sections on behalf of Metasyn

Date	To	From	Description
02/22/2000	A. Eric Jones, FDA	Meri C. Bloom, EPIX	Mail: Information on the 12-lead Holter Monitor currently used in Clinical Study Protocols MS-325-07 (renal population) & MS-325-06 (warfarin/safety protocol)
03/03/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Message was left at agency regarding EPIX letter sent requesting a copy of FDA meeting minutes EOP 2 meeting held in March of 1999
03/06/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Agency phoned to confirm that we received faxes sent on several dates
03/06/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Official minutes from the March 3, 1999 industry meeting
03/10/2000	Rubynell Jordan, FDA	Susan Flint, EPIX	Phone: A memo with dates in 1999 documenting phone calls to the agency that were not previously documented
03/20/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: EPIX requesting meeting minutes from the AngioMark CMC Meeting of 03/30/1999
03/22/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Meeting minutes from March 30, 1999 (CMC meeting)
04/14/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Message left for Agency requesting a response regarding EPIX letter from 01/14/2000
04/18/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: EPIX letter of 1/14/2000 to the agency has been reviewed, the Medical officer had no problems or comments
07/03/2000	Susan Flint, EPIX	CSO, FDA	Phone: Dr. Jones will not allow implementation of the revised Phase 3 Protocol – efficacy endpoints not acceptable
07/19/2000	Susan Flint, EPIX	CSO, FDA	Phone: Dr. Jones has comments and wants to schedule T-con in August
07/21/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: For Serial #075 addressing the P2 blinded read protocol for evaluating the dose-response MRA
07/31/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: CSO called to confirm we received their recently faxed questions on the blinded read protocol

Date	To	From	Description
07/31/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Agency called to confirm the Phase 3 Protocol submitted was our original protocol and not the revised protocol that Dr. Jones just made comments to
08/08/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Left VM for Archana regarding an update on the status of EPIX meeting with the agency and regards to the Phase 3 Protocol
08/14/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: EPIX requested additional information regarding meeting
08/22/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Regarding Phase 3 protocol amendment, EPIX request a complete set of FDA written comments.
08/24/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Archana confirmed comments were to be sent to us and reconfirmed Dr. Jones wanted to speak with Susan/EPIX
08/24/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Requesting response for Serial #078 P3 Protocol comments
08/24/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Regarding Serial #078 addressing the P3 protocol (clinical comments)
08/31/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Checked on status of FDA's internal meeting and Agency requested clarification of which Phase 3 protocol was actually the most current
09/05/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Agency does not intend on giving statistical comments regarding the proposed Phase 3 protocol due to the confusion they had of which Phase 3 protocol was most current
09/06/2000	Archana Reddy, FDA	Susan Flint, EPIX	Fax: Per FDA request, a copy of the previous FDA fax. Also included the cover letter of EPIX response to the original fax. EPIX request to receive that Statistical comments on the revised Phase 3 Protocol (Serial #078)
09/11/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: EPIX request a T-con with Dr. Love or Dr. Jones for clarification on a few issues
09/13/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: 11 additional copies of the annotated Phase 3 protocol from our May submission requested

Date	To	From	Description
09/14/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Request for 8 copies of our clinical response from last October to their initial list of questions. Meeting with FDA may be delayed due to our numerous calls to the FDA; expressed by Archana
09/19/2000	Archana Reddy, FDA	Susan Flint & Steve Knight, EPIX	Phone: Meeting scheduled for October 3, 2000. Archana mentioned requesting phone conference would delay a face to face meeting with the agency
09/26/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Archana left a VM with a T-con date of October 4, 2000
10/17/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Called to ask when we would submit our meeting minutes from the T-con and the second Phase 3 protocol.
11/01/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Templates of sample safety tables as requested during the Oct. 4 T-con
11/15/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Left voicemail requesting status of the CMC meeting
11/28/2000	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Informed FDA that EPIX hoped to start Phase 2 blinded reads soon and needed medical comments (Serial #101). Also requested T-con (10/4) meeting minutes
12/07/2000	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Phase 2 protocol was being actively reviewed. CMC meeting not necessary.
12/27/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Minutes from the teleconference held on October 4, 2000
12/27/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Request for response to comments to Serial #090
12/27/2000	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Request for response to clinical/statistical comments for Serial #095
01/02/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Called to confirm receipt of revised Phase 3 protocol and requested meeting or tel-con to confirm that their concerns raised in the 10/4 meeting were successfully addressed
01/24/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: FDA still reviewing Phase 3 protocol. EPIX going to implement the Phase 2 blinded read protocol

Date	To	From	Description
01/25/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: No medical comments on the Phase 2 blinded protocol, but needs to be reviewed for statistics
02/07/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Called to discuss status of Phase 3 protocol – comments should be ready middle of next week
02/12/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Left a voicemail stating that the revised Phase 3 protocol would be sent to clinical sites on Fri (2/16) since it was past the 30 day review period
02/13/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Dr. Yaes and Dr. Sobhan were informed about the plan to send Phase 3 protocol to sites. It is still under review
02/16/2001	Susan Flint, EPIX	Archana Reddy, FDA	Phone: Left voicemail stating statistical comments on Phase 3 protocol would be faxed and FDA received the imaging parameters pages
02/20/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: EPIX did not receive fax (statistical comments)
02/20/2001	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Statistical comments regarding Serial #105
02/21/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Requested clarification on faxed questions
02/27/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Called for update on the status of the clinical comments on the revised Phase 3 protocol
03/01/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Requested a t-con to discuss Serial #109
03/09/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Requested updates on FDA comments and asked a few questions. FDA asked for questions to be faxed.
03/12/2001	Archana Reddy, FDA	Susan Flint, EPIX	Fax: Questions for the Division concerning plans on filing the NDA
03/15/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: FDA received fax and will give us feedback on Phase 2 protocol within a week and a half
04/04/2001	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Request for response to clinical comments for Serial #105
04/13/2001	Archana Reddy, FDA	Susan Flint, EPIX	Phone: Inquiry in regard to EPIX's previously sent questions; CTD and Electronic submissions; Plan outlined for additional body regions was acceptable to Dr. Jones

Date	To	From	Description
05/23/2001	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Clinical comments for Serial #106
05/23/2001	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Clinical comments for Serial #084
05/23/2001	Susan Flint, EPIX	Archana Reddy, FDA	Fax: Clinical comments for the sponsor (Serial #117 & #118) with a request for response
07/11/2001	Susan Flint, EPIX	FDA	Phone: Should expect a call on July 20 for the date of our End of Phase 2 Meeting with the FDA
07/19/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: CMC, pharm/tox, clinical pharmacology, and clinical-stats comments for EOP2 meeting
07/19/2001	Susan Flint, EPIX	FDA	Phone: EOP2 meeting has been scheduled for Tuesday, Aug 28
07/24/2001	Susan Flint, EPIX	Kyong Cho, FDA	Mail: Meeting confirmation and tentative list of participants
07/24/2001	Eric Jones, FDA	Susan Flint, EPIX	Phone: Phase 3 protocol discussion – EJ requested dose justification
08/02/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: Microbiology comments on submission dated 07/31/2001
08/07/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: Requested clarification of additional body regions in the next Phase 3 protocol
08/08/2001	Susan Flint, EPIX	Thuy Nguyen and Eric Jones, FDA	Phone: Questions pertaining to the lack of Phase 2 dose ranging data on the feet
08/08/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: No specific person will be the contact for eNDA, still reviewing Phase 2 meeting package, wanted to confirm there are no additional questions for Phase 2 meeting
08/09/2001	Thuy Nguyen, FDA	Susan Flint, EPIX	Phone: Asked if Dr. Jones had reviewed dose justification for the feet
08/09/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: EPIX will provide memo that outlines the clinical development of MS-325
08/24/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: Tentative list of FDA participants for the T-con on Aug 28, 2001
08/28/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: Comments on clinical/statistics, clinical pharmacology, and pharmtox. Particular comments on QT and uninterpretable scans.

Date	To	From	Description
08/28/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: Preliminary responses to Agency's meeting questions, to be discussed at the August 28 teleconference at 2:30pm
08/30/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Fax: Clinical comments in reference to Serial #109
11/02/2001	Thuy Nguyen, FDA	Susan Flint, EPIX	Phone: Informed agency that the MS-325-13 protocol will go into effect next week
11/05/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: Message was relayed to agency regarding the start of trial MS-325-13
11/20/2001	Susan Flint, FDA	Thuy Nguyen, FDA	Fax: Discussion held on 08/28/2001 regarding the sponsor's meeting questions and the division's preliminary responses in reference to the meeting package of 07/31/2001
12/05/2001	Thuy Nguyen, FDA	Susan Flint, EPIX	Phone: Informed agency the Renal Protocol will begin this week in clinic
12/10/2001	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: Thanked EPIX for the message and that the information was passed along
02/20/2002	Thuy Nguyen, FDA	Susan Flint, EPIX	Phone: In response to EPIX's 2/14/02 question
08/22/2002	Susan Flint, EPIX	Thuy Nguyen, FDA	Phone: Request for EPIX to resubmit Serial #165 which was submitted on 8/15/02 because of missing CVs for Principal Investigators. S. Flint returned the call to explain that EPIX submits only the PI CV for the original filing of a 1572.
09/13/2002	Thuy Nguyen, FDA	Susan Flint, EPIX	Phone: Called to request a current list of all agency personnel assigned to review MS-325. T. Nguyen returned the call and stated that Captain James Moore is EPIX's new Project Manager and Moore should be contacted for a list of reviewers
09/16/2002	Susan Flint, EPIX	James Moore, FDA	Phone: J. Moore notified S. Flint that he hopes to get back to S. Flint by the end of the week with the current personnel list

Date	To	From	Description
10/08/2002	Susan Flint, EPIX	James Moore, FDA	Phone: 3 new members: Pharm/Tox – Dr. Adebayo Laniyono, Micro – Dr. David Hussong, Clin-Pharm – Dr. Christy John. Also the agency asked if Dr. Frasmo de la Pena-Almageur had any additional training
12/04/2002	James Moore, FDA	Susan Flint, EPIX	Phone: Moore wanted to confirm that we only wanted to include the 1572s. Flint left a VM confirming Serial #171 was meant to only contain the 1572s
12/04/2002	James Moore, FDA	Susan Flint, EPIX	Email: Confirmed Serial #171 should only contain new or revised FDA forms 1572
02/25/2003	Susan Flint, EPIX	James Moore, FDA	Phone: Seeking clarification on recent filing Serial #176 regarding 1572 updates which did not include CVs of sub-investigators
02/27/2003	Kay Kang, FDA	Robert Morgan, EPIX	Phone: Introducing Robert Morgan as new EPIX Regulatory contact. Also several questions from EPIX as well as a June/July timeframe for an anticipated submission
03/24/2003	James Moore, FDA	Robert Morgan, EPIX	Phone: FDA does not usually accept requests to meet prior to the submission of Pre-Meeting package, but has modified that policy and will need a copy of questions that EPIX will be asking at the meeting in advance. JM also wanted a list of potential meeting dates
04/08/2003	James Moore, FDA	Robert Morgan, EPIX	Phone: RM called FDA to inform them pre-NDA package is en route and determine if a date has been selected for the meeting. Meeting is on May 20, 2003.
04/10/2003	Robert Morgan, EPIX	Kyong Kang, FDA	Mail: States that EPIX requested a "Type B meeting" which is tentatively scheduled for May 20, 2003. Provided a checklist of items that FDA would like included in the meeting package.

Date	To	From	Description
04/10/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: EPIX to send replacement page for Pre-NDA package. Mr. Moore requested (16) additional copies for FDA attendees at Pre-NDA meeting. Mr. Moore informed EPIX that only one Pre-NDA meeting can be granted.
04/15/2003	James Moore, FDA	Robert Morgan, EPIX	Email: Confirmed 5/20/03 meeting date with FDA. MS-325 Pre-meeting package checklist addressed.
05/05/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: Confirming receipt of Pre-NDA meeting packages, and that FDA has all the information they require
05/13/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: Response to FDA's request for an electronic copy of the slides for the Pre-NDA meeting
05/14/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: Division response to questions contained in EPIX's meeting package for IND 51,172 MS-325 dated April 7, 2003; submitted to the division for discussion at the Pre-NDA Industry meeting scheduled for May 20, 2003. FDA does not have authority to issue Pediatric Waiver.
05/16/2003	James Moore, FDA	Debra Suckney, EPIX	Email: EPIX to send the Follow Up Safety Report to the 15-day Safety Report
05/18/2003	James Moore, FDA	Debra Suckney, EPIX	Email: Submission of electronic copy of the slides EPIX plans to present at the Pre-NDA meeting scheduled for May 20, 2003.
05/21/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: Attendee list for pre-NDA meeting of May 20, 2003
05/27/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: Reviewing statistician's request for specific formatting of SAS data files for EPIX Medical's NDA submission for MS-325
05/29/2003	James Moore, FDA	Debra Suckney, EPIX	Email: slides from pre-NDA meeting of May 20, 2003
05/29/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: Notification of sending slides from pre-NDA meeting via email, also additional questions
05/30/2003	Debra Suckney, EPIX	James Moore, FDA	Email: Confirms receipt of slides from pre-NDA meeting

Date	To	From	Description
05/30/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: Questions for FDA regarding whether EPIX needs to send the NDA paper review copy in defined colored binders, and which field office EPIX would be submitting to for the CMC section of the NDA
06/18/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: FDA Meeting minutes from pre-NDA meeting on May 20, 2003
06/19/2003	James Moore, FDA	Debra Suckney, EPIX	Phone: Confirmed receipt of Serial #190. Will not need EPIX training for now, but probably after eNDA submission. Mentioned that EPIX should not expect written response regarding abbreviated study reports b/c it's EPIX's decision in the end. Will let EPIX know with regard to training.
07/02/2003	James Moore, FDA	Robert Morgan, EPIX	Email: Informal note clarifying what EPIX means by abbreviated study report and our intentions to submit them in upcoming NDA
07/08/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: FDA Clinical comments regarding Serial #190
07/22/2003	EPIX	FDA	Official FDA Fax of Trade Name Review by Office of Drug Safety (Unable to locate documentation)
08/21/2003	Debra Suckney, EPIX	Sally Loewke, FDA	Mail: Declined request for meeting b/c request is premature. EPIX can appeal this decision.
09/26/2003	James Moore, FDA	Debra Suckney, EPIX	Email: Confirm Biostatistics T-con for Sept 30, 2003 and provided call-in number
09/26/2003	Debra Suckney, EPIX	James Moore, FDA	Email: Thank you email in response to DS's email
10/07/2003	James Moore, FDA	Debra Suckney, EPIX	Email: List of attendees for Sept. 30, 2003 T-con with FDA
10/08/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: Proposed data set transformation based on the review of SAS data set (EFFANLYS) and T-con on Sept. 30, 2003
10/09/2003	Debra Suckney, EPIX	James Moore, FDA	Email: Request confirmation of what is acceptable to FDA in terms of eNDA submission

Date	To	From	Description
10/16/2003	James Moore, FDA	Debra Suckney, EPIX	Email: A thank you email to James Moore in response to questions answered regarding eNDA
10/16/2003	Debra Suckney, EPIX	James Moore, FDA	Email: Send 15 copies of summary volume 1.1. Send review copy of NDA for each discipline (clinical pharmacology, etc.).
10/16/2003	James Moore, FDA	Debra Suckney, EPIX	Email: Forwarded email original sent on Oct 9, 2003 – this was a follow-up email regarding number of paper copies to be submitted for each discipline, etc.
10/17/2003	Debra Suckney, EPIX	James Moore, FDA	Fax: Meeting minutes from Sept 30, 2003 T-con – formatting of the data sets were the main topics of discussion
12/02/2003	James Moore, FDA	Debra Feldman, EPIX	Email: How will FDA accept eNDA? b/c it won't all fit into five CDs, per guidance
12/14/2003	James Moore, FDA	Debra Suckney, EPIX	Email: Logistics information on when eNDA will be delivered, when paper copy will be sent, trainings for reviewers, etc.
12/15/2003	Debra Suckney, EPIX	James Moore, FDA	Email: Response to question concerning colored binders
****Break in correspondence due to all correspondence being submitted to the NDA****			
05/05/2005	Robert Morgan, EPIX	Kaye Kang, FDA	Phone: New FDA PM for EPIX is Thuy Nguyen – EPIX has worked with her previously. RM confirmed that FDA 'reog' will occur in July.
01/09/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: AS informed JM of a change in regulatory staff at EPIX and stated that she will be the main point of contact at EPIX
03/10/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: Request to revise IB to remove misleading statements on efficacy and safety of MS-325
11/07/2007	James Moore, FDA	Margaret Uprichard, EPIX	Fax: EPIX meeting minutes from the 10/30/07 T-con to discuss the Divisions' fax regarding Statistical Handling of uninterpretable vessel-segments in the Vasovist Re-read protocol
****Break in correspondence due to all correspondence being submitted to the NDA****			

Date	To	From	Description
01/22/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: **Please reference NDA 21-711** FDA Fax of Correction McNemar's Equation
01/22/2008	Grace Carmouze, FDA	Margaret Uprichard, EPIX	Email: EPIX request for confirmation regarding the appropriate regulatory mechanism for review of the December 20, 2007 teleconference
01/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Correction to SAP requested by the Division
01/31/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax, Mail: **Please reference NDA 21-711** Agency's faxed response to December 21, 2007 submission for NDA 21-711
01/31/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX request for clarification on the Division's classification of the re-submission in response to Action Letters w/ reference being made to the Agency's Action Letter fax of January 29, 2008
01/31/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Reference is being made to the Division's Action Letter of January 29, 2008. The Division's response to EPIX request clarifying that the re-submission will be classified upon its arrival w/ reference to the Final blinded re-read of 12/21/07
04/16/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Teleconference scheduled for June 5, 2008 to discuss NDA resubmission, with questions from EPIX with regard to the Division's NDA review team.
05/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Fax: Response to division's request for EPIX to provide questions for the June 5, 2008 T-con
05/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX's previously submitted questions with regard to the June 5, 2008 teleconference
06/04/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: **Reference NDA Correspondence** Division's fax of draft responses and comments to questions from EPIX in preparation for the T-con scheduled for June 5, 2008, with regard to NDA 21-711 re-submission

Date	To	From	Description
06/04/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: 2 additional attendees for June 5, 2008 T-con with division regarding NDA Resubmission. Shahidah Muhammad and Rebecca Warwick
06/06/2008	James Moore, FDA	Margaret Uprichard, EPIX	Mail: Sent to the Division with Request for Division's attendee list, regarding the June 5, 2008 NDA Resubmission T-Con
06/10/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Response to EPIX's question: Has the Division issued a Pediatric Waiver and if the Division would prefer to Receive the request as part of the NDA Resubmission
06/11/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Division's confirmation response with regard to Dr. Rieves no longer serving as "acting" Division Director but is now the "Division Director."
06/13/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX's version of the minutes from the June 5, 2008 T-Con, requested by Division
06/16/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: From the Reviewing Chemist, with regard to the NDA 21-711 scheduled resubmission
06/26/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Maggie's email notifying the Division that the NDA Resubmission for Vasovist will be submitted on Monday, June 30, 2008 2 weeks ahead of the scheduled given date.
07/01/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Notification that the NDA Resubmission Package was sent and delivered via Fed-Ex from EPIX to the Division's document room.
07/02/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: June 5, 2008 Meeting minutes between EPIX and the Division regarding the Meeting Package for the Vasovist Resubmission
07/16/2008	James Moore & Kyong Kang, FDA	Margaret Uprichard, EPIX	Email, Fax: NDA Resubmission Index and Cover Letter
07/17/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX Request for an update on the acknowledgement of receipt letter for the Vasovist NDA Resubmission including the classification and review goal date

Date	To	From	Description
07/18/2008	James Moore, FDA	Maggie Uprichard, EPIX	Email: The status of FDA acknowledgement of receipt letter for the Vasovist® NDA Resubmission
07/23/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Division's email verification that the Acknowledgement letter for the NDA 21-711Vasovist® Resubmission will be signed and faxed no later than 07/24/2008
07/24/2008	Margaret Uprichard, EPIX	James Moore, EPIX	Fax: Division's Acknowledgement Letter, of the NDA 21-711 Vasovist® Resubmission dated June 30, 2008, with a class 2 response to the November 21, 2005 action letter. The user fee goal date is set for December 31, 2008.

EPIX Pharmaceuticals, Inc.
VASOVIST® MS-325; NDA 21-711
Submission Index

YEAR	DATE	TO	FROM	DESCRIPTION
2003	**December 12**	Florence Houn-FDA	Robert Morgan-EPIX	Original NDA Submission
2004	**January 30**	Patricia Stewart-FDA	Robert Morgan-EPIX	General Correspondence: EPIX request clarification of the Review Priority Classification designation included in the acknowledgement letter
	February 06	Hsien Ju-FDA	Robert Morgan-EPIX	Response to Request for Information: EPIX response to the Division's request (during 02Feb04 teleconference) a listing of all Phase III clinical sites with contact information, No. of patients enrolled at each site, No. of adverse events at each site
	February 10	Hsein Ju-FDA	Robert Morgan-EPIX	Response to Request for Information: Breakdown of Phase III AE's according to study, site and patient No. along with individual list of AE's per patient. Submission via Email
	February 10	Hsein Ju-FDA	Robert Morgan-FDA	Response to Request for Information: Division's action items resolution with regard to the EPIX electronic NDA for VASOVIST training of January 15, 2004, materials in this submission are: resolution; EPIX meeting minutes, meeting presentation overheads, identification of scanned versus electronic documents in the eNDA, draft labeling as MS word files, CD with requested information

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**February 18**	Hsein Ju- FDA	Robert Morgan-EPIX	Response to Request for Information: Images and supporting data requested for use in discussions at FDA (sent in 4 separate packets due to size of each file). Images are samples that were used for blinded read training. Data tables (Image Interpretation for MRA and XRA) extracted from Listings in NDA and correspond to each patient used in the presentation
	February 27	James Moore-FDA	Debra Feldman-EPIX	Response to Request for Information: EPIX response to Division's Pharmacology reviewer's questions regarding the effects of fatty meals on MS-325
	March 11	James Moore-FDA	Debra Feldman-EPIX	Response to Request for Information: Submission of supplementary efficacy database following description provided in 09Dec03 email correspondence and confirmed by Dr. Mucci and R. Weisskoff at the 15Jan04 eNDA training session
	March 12	Sally Loewke-FDA	Robert Morgan-EPIX	General Correspondence: EPIX acknowledgement of Division's 74-day response letter as well as Division's decision to grant standard review and not priority review. EPIX wanted to make short clarifications of several issues.
	March 30	James Moore-FDA	Robert Morgan-EPIX	Response to Request for Information: Pharmacology-EPIX response to the Division's Reviewing Pharmacologist question (dated March 24, 2004) regarding study PTR 2003-12 for alternative chronic renal impairment models to be investigated for future studies and which animal species would be used

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**April 14**	Sally Loewke-FDA	Debra Feldman-EPIX	120-Day Safety Update: Submission of NDA Item (9) in electronic format (Paper review copy to follow within 5 business days) Inclusive: Clinical Study Report MS-325-18, Labeling, Updated Annotated Draft Package Insert, Clinical; full MS-325-12 study report, Case report tabulations; updated data sets and CRT TOC (to include MS-325-18)
	April 20	Roy Blay-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: Study Information requested by the Division to support audits of the pivotal trials for NDA 21-711, via 6 sets of CD's, for studies; MS-325-12, MS-325-13, MS325-14, MS-325-15
	April 29	James Moore-FDA	Michelle Younis-EPIX	Response to FDA Request for Information: Additional copies of120-Safety Update submission Volume 1 & 2 marked desk copy
	April 30	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical- EPIX response to Division's question referring to Study MS-325-01A & MS-325-01C (in original NDA submission of December 15, 2003) requesting QT data to be summarized Note: Cover Letter incorrectly dated March 30, 2004
	May 14	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical-A Detailed summary for each patient who experienced Syncopal Episodes in Clinical Development , copies of all initial and follow-up IND safety reports and analyses from any IND annual reports on those 3 patients whose Syncopal Episodes were labeled as SAE

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**June 3**	James Moore-FDA	Debra Feldman-EPIX	Response to Request for Information: Supplementary Database-Division request additional copies of the previously submitted (March 11, 2004) Supplementary Database summarizing the efficacy results of the four Phase III trials of MS-325
	June 11	James Moore-EPIX	Debra Feldman-FDA	Response to FDA Request for Information: Clinical-EPIX response to the Clinical Reviewer's questions of Oxygen Saturation levels in 19 patients pre- and post MS-325 administration as well as the Adverse Event Data
	June 29	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical Requests 1 & 2- Primary Analysis, Possible Secondary Analyses
	July 16	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical- 3 questions with regard to quantitative ST-segment measurements in 17 patients
	July 16	James Moore-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: Pharmacology- EPIX response to Division's request for information on the status of the Rat Renal Impairment Study
	August 6	George Mills-FDA	Debra Feldman-EPIX	Response to questions asked via phone by James Moore (FDA August 4, 2004) regarding the Statistical Analysis Plan for Pivotal Trials
	August 11	Roy Blay-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Pivotal Trials- EPIX response with disc's containing a listing of adverse events and vital sign data by patient, for clinical sites; MS-325-14 & MS-325-15

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**August 12**	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical- EPIX response to Division's request for; Justification for selecting 2D-TOF as the standard non-contrast MRA technique for all arterial regions, Average effect analysis, Different analytical strategy in handling of uninterruptable MRA images in primary data analysis, Vessel segment analysis, Subgroup analysis, Agreement between XRA readers, Aneurysms endpoint, Clarification regarding steady-state image, Data resubmission request
	August 12	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical- EPIX response of statistical questions regarding the variables provided in the MS-325-14 (Renal MRA) trial as well as two excerpts from the Clinical Study Report
	August 19	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical- EPIX response to Division's request for the resubmission of MS-325Supp_Data.xpt dataset that was originally submitted on March 11 2004
	August 20	George Mills-FDA	Robert Morgan-EPIX	General Correspondence: VASOVIST Name Reconsideration-EPIX requesting DMETS to reconsider its recommendation and for the Division to approve the use of VASOVIST as the proprietary name for MS-325
	August 20	James Moore-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: CMC-EPIX response to Division's request that include additional Post-Approval stability commitments

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**August 30**	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical-Resubmission of EPIX response to agency regarding MS-325Supp_Data.xpt dataset that was originally submitted March 11
	September 1	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Per request of Dr. George Mills, these paper copies of the electronic blinded read Case Report Forms constitute the required submission coupled along with sampling of images from the blinded read for studies-MS-325-12, -13, -14, and -15
	September 2	George Mills-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical- EPIX response to Statistical reviewer's questions regarding confidence intervals for the Vessel-Weighted statistics for the four Phase II studies
	September 2	James Moore-FDA	Robert Morgan-EPIX	Response to request for information dated 30Aug2004 regarding zinc and zinc fosveset levels in moderate and severe renally impaired subjects as compared to healthy normals. Note: Fax sent from Debra Feldman to James Moore
	September 8	George Mills-FDA	Debra Feldman-EPIX	General Correspondence: EPIX Name Change-EPIX notifying division of name change from EPIX Medical, Inc. to EPIX Pharmaceuticals, Inc.
	September 10	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Clinical and Statistical- EPIX response to Division's Clinical and Statistical Reviewer's questions regarding the efficacy of VASOVIST ™

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**September 10**	James Moore-FDA	Debra Feldman-EPIX	Response to request for info made at the blinded read training at FDA on 2Sept2004. Includes Imaging timelines for each of the ph. III protocols
	September 14	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information-Statistical (Different Sample Size) EPIX response to Statistical Reviewers Comment/Questions regarding Study #12 and Study #13 and the doubling of sample sizes
	September 14	George Mills-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical- EPIX response to Division's request for Statistical information during the August 30, 2004 T-Con regarding modifications to the analysis of uninterpretable vessels
	September 15	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: EPIX response to the Division's Clinical Reviewer (during Blinded Read training on September 2, 2004) regarding List of Patients US vs. Non US enrollment in the four Phase III studies
	September 28	George Mills-FDA	Robert Morgan-EPIX	General Correspondence: Explanation of acquiring non contrast MRA during Phase III trials, Provided literature overview to rate uninterpretable non-contrast studies in clinical practice
	October 1	George Mills-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: EPIX provides results from naming comparison study(VASOVIST vs. MAGNEVIST)

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**October 6**	James Moore-FDA	Debra Feldman-EPIX	General Correspondence: EPIX submitting an Amendment to Item 2 of the NDA submission with revised Labels and Packaging
	October 11	James Moore-FDA	Debra Feldman-EPIX	General Correspondence: Resubmission of the Amendment to Item 2 of the NDA submission with revised labels and Packaging, EPIX inadvertently failed to include the revised 10mL sample label
	October 12	James Moore-FDA	Robert Morgan-FDA	Teleconference Meeting Minutes: Meeting Minutes from the October 7, 2004 teleconference between EPIX and FDA. EPIX to provide Division with additional information over the next 2 weeks, plan to submit responses as they are completed and not wait until October 22nd to send a single response.
	October 13	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Statistical Questions- EPIX response to statistical reviewer's questions from October 7, 2004 Teleconference regarding uninterpretables for study MS-325-14
	October 22	George Mills-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: EPIX response to questions from October 7, 2004 teleconference regarding 6 major points raised; Efficacy (uninterpretables), dynamic vs. steady state & safety (hemoglobin) issues

YEAR	DATE	TO	FROM	DESCRIPTION
2004	**October 27**	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Pharmacology- EPIX response to Division's reviewing pharmacologist request to provide the individual data for the Study Report No. A10333
	November 3	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Re-submission of individual data for study no. A10333 via email and FedEx, due to broken CD in original submission (October 27, 2004)
	December 1	James Moore-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: EPIX Response to Divisions Request (via voicemail November 28, 2008) for a listing of Key Teleconferences regarding NDA 21-711 (EPIX/FDA) that has occurred from June 2004-December 1, 2004
	December 29	George Mills-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: EPIX response to questions raised by the Division's Clinical Pharmacology Reviewer regarding the hypothesis that transmetallation and increased excretion on Zn correspond directly to the stability of the Gd complex
	December 29	George Mills & Julie Beitz-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: Statistical – EPIX is providing alternative analyses of the data previously submitted to the NDA that are responsive to the Division's questions regarding various methodologies for the handling of uninterpretable exams in the determination of sensitivity and specificity

YEAR	DATE	TO	FROM	DESCRIPTION
2005	**January 18**	Julie Beitz-FDA	Robert Morgan-EPIX	General Correspondence- EPIX acknowledges receipt of Action Letter (January 12, 2005)-Approvable, EPIX Notifying Division of intent to Amend NDA No. 21-711
	February 4	James Moore-FDA	Debra Feldman-EPIX	General Correspondence, Meeting Minutes: EPIX generated Meeting Minutes from the December 7, 2004 Teleconference between EPIX and FDA to discuss the review of the NDA
	May 23	George Mills-FDA	Robert Morgan-EPIX	Complete Response to FDA's Approvable Letter: EPIX complete response to the January 12, 2005 FDA Action Letter for MS-325
	July 13	George Mills-FDA	Robert Morgan-EPIX	Other: Meeting Request- EPIX requests Type B meeting with Division for the 4th week in August 2005 to discuss the design/implementation of Phase 4 study to investigate the relative contributions of the dynamic and steady-stage images in the use of MS-325
	August 1	George Mills-FDA	Robert Morgan-EPIX	Pre- Meeting Information Package: EPIX is submitting an information package to provide background for the requested meeting with division to discuss the study concepts for evaluating in phase IV the relative contributions of dynamic and steady-state MS-325 contrast-enhanced images in the diagnosis of vascular disease

YEAR	DATE	TO	FROM	DESCRIPTION
2005	**August 24**	George Mills-FDA	Robert Morgan-EPIX	Response to FDA Request for Information: Statistics; Uninterpretables/Reanalysis-EPIX response to Division's Fax of August 10, 2005 requesting additional data and analysis from MS-325 clinical trials primarily relating to uninterpretability (rates of ininterpretable images from on-site reads and blinded reads)
	September 1	George Mills-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Pharmacology- EPIX response to Division's faxed request of August 24, 2005 for additional data for Report A25681
	October 10	George Mills-FDA	Debra Feldman-EPIX	Response to FDA Request for Information: Pharmacology- EPIX response to Division's faxed Request dated October 4, 2005 with eight tables that contain data for report A25681
	December 01	Karen Weiss-FDA	Robert Morgan-EPIX	Other: 10Day Response to FDA Approvable Letter-EPIX agrees to extend the review period so it can determine whether to respond further, EPIX intends to request a meeting (as encouraged by Division) with the Division of Medical Imaging and Hematology, EPIX also intends to appeal the Division's decision regarding VASOVIST and to request an advisory committee prior to resolution of, and as part of, its appeal

YEAR	DATE	TO	FROM	DESCRIPTION
2005	**December 5**	George Mills-FDA	Robert Morgan-EPIX	General Correspondence: Meeting Request- EPIX request for a "Type A" meeting with the Division in response to the November 21, 2005 approvable letter regarding VASOVIST. EPIX proposes a Two-Part agenda for the meeting
	December 21	George Mills-FDA	Debra Feldman-EPIX	General Correspondence: Meeting Package- EPIX providing Division with a background information package for the scheduled January 5, 2006 Type A meeting to discuss details of deficiencies identified in the approvable letter
2006	**January 3**	James Moore-FDA	Debra Feldman-EPIX	General Correspondence: Revised Agenda- EPIX providing Division with a revised agenda for the January 5, 2006 Type A meeting.
	January 12	James Moore-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX Meeting Minutes-Meeting Minutes generated by EPIX from the January 5, 2006 Type A meeting with the Division
	January 27	James Moore-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX informs Division that Aarati Sridharan will be the new point of contact, Debra Feldman and Robert Morgan are no longer employed at EPIX
	February 2	George Mills-FDA	Aarati Sridharan-EPIX	General Correspondence: Meeting Request- EPIX requests a meeting with the Division to discuss the design of new clinical trial that may be used to prove efficacy. EPIX also sends a Meeting Request Information Package

YEAR	DATE	TO	FROM	DESCRIPTION
2006	**February 17**	George Mills-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX request to change Division's meeting minutes of its January 5, 2006 meeting, EPIX believes that some language in these minutes should be modified to better reflect important statements made at the meeting
	March 3	George Mills-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX submitting its Information Briefing Package for its scheduled April 5, 2006 meeting to discuss a draft clinical protocol
	March 9	James Moore-FDA	Aarati Sridharan-EPIX	Response to FDA Request for Information: EPIX response to Division's request for a list of questions for it's scheduled April 5, 2006 to discuss a draft clinical protocol for MS-325
	March 29	James Moore-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX submitting a revised list of attendees for its scheduled April 5, 2006 meeting, also attached is a brief Bio of Dr. Charles Metz
	April 3	James Moore-FDA	Aarati Sridharan-EPIX	General Correspondence: EPIX providing Division with Agenda for its April 5, 2006 meeting, topics to be covered are in light of the Division's comments and information requests that were sent on March 31, 2006

YEAR	DATE	TO	FROM	DESCRIPTION
2006	**May 31**	George Mills-FDA	Aarati Sridharan-EPIX	Response to FDA Request for Information: Per Division's request, EPIX has reviewed its safety database of nephrogenic fibrosing dermopathy (NFD) or similarly severe skin and no reports have been identified
	June 30	Kim Colangelo-FDA	Aarati Sridharan-EPIX	EPIX submits a Formal Dispute Resolution Request to appeal the decision of the Office of Oncology Drug Products ("OODP") not to approve EPIX NDA for its imaging drug, this appeal is also being submitted to John K. Jenkins because the decision not to approve MS-325 in this review cycle was made at the Office level by the Deputy Director
	September 27	John Jenkins-FDA	Andrew Uprichard & Philip Graham-EPIX	General Correspondence: Meeting Request- EPIX requests meeting to discuss FDA's reasons of denial regarding EPIX Formal Dispute Resolution Request (June 30, 2006) to the Office of Oncology
	November 30	Karen Weiss-FDA	Aarati Sridharan-EPIX	EPIX letter to follow-up to the December 1, 2005 letter, in this letter EPIX agreed to an extension for a time period equal to "the length of time necessary to meet with the Division and the time to complete its appeal, including multiple appeals if needed, plus 10 days after completion of the entire process, to respond further under 314.110(a).". If the extension must be defined in time, EPIX requests an additional 12 month extension

YEAR	DATE	TO	FROM	DESCRIPTION
2007	**February 27**	Kim Colangelo-FDA	Andrew Uprichard-EPIX	Formal Dispute Resolution Request & Meeting Request: EPIX submits formal dispute resolution request to appeal the Office of New Drugs decision not to approve VASOVIST (August 25, 2006 decision) as well as a request for a meeting with Dr. Galson and other Division personnel to discuss the issues described in the appeal document as well as a briefing package
	May 17	Grace Carmouze-FDA	Andrew Uprichard-EPIX	Response to FDA Request for Information: EPIX responds to questions from Grace Carmouze's call to Aarati Sridharan on May 15, 2007 regarding questions raised at the May 8, 2007 meeting. EPIX providing clarification of the key discussion points during the meeting
	May 21	R. Dwaine Rieves-FDA	Aarati Sridhara-EPIX	Response to FDA Request for Information: EPIX responses to questions from the May 8, 2007 meeting and Dr. Blank's questions of May 3, 2007. Also included is a copy of two periodic Safety Update Reports submitted to the EMEA on May 22, 2006 and November 20, 2006, per Dr. Blank's post-meeting discussion with Dr. Andrew Uprichard
	June 5	R. Dwaine Rieves-FDA	Aarati Sridharan-EPIX	General Correspondence: Additional Statistical Analyses that address some points raised during the teleconference by Dr. Anthony Mucci, to the June 01, 2007 teleconference with Dr. Douglas Throckmorton, and to the email of June 4, 2007

YEAR	DATE	TO	FROM	DESCRIPTION
2007	**August 23**	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	General Correspondence: Protocol for Blinded Re-Read- Per Dr. Throckmorton's recommendation, EPIX is submitting the following Draft protocol MS-325-12/13R as well as the Statistical Analysis Plan and blinded reader training materials, this protocol is to confirm the efficacy of VASOVIST demonstrated in the two AIOD studies
	August 30	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Request for Type A Meeting: EPIX requesting a Type A meeting with the Division to discuss and obtain agreement on the protocol and Statistical Analysis plan of the Phase III study No's MS-325-12 and MS-325-13
	October 15	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Response to FDA Request for Information: EPIX submitting written response to Division's preliminary comments/questions of October 10, 2007 regarding the August 23, 2007 submission of the blinded re-read images from Phase III: MS-325-12 & MS-325-13
	October 26	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	EPIX Meeting Minutes from the October 23, 2007 meeting with the division, inclusive are the slides presented at the meeting along with EPIX version of the meeting discussion, a copy of the August 30, 2007 meeting request submission and a copy of the October 22, 2007 Division Fax
	November 7	R. Dwaine Rieves & James Moore-FDA	Margaret Uprichard-EPIX	Minutes from the October 30, 2007 Teleconference minutes regarding the FDA Fax: Statistical vessel-segments in the re-read

YEAR	DATE	TO	FROM	DESCRIPTION
2007	**November 14**	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	EPIX Submits a Revised Vasovist™ Blinded Re-Read Protocol, (Reader Training Guidelines & Statistical Analysis Plan)
	December 21	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	EPIX submits a Final Blinded Re-Read Protocol (Statistical Analysis Plan, Blinded Reader Training Guidelines)
2008	**January 23**	James Moore & R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	An administrative amendment to protocol MS-325-12/13R correcting the equation with regard to the December 21, 2007 submission
	April 3	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	General Correspondence: EPIX requests a Teleconference with the Division to discuss and obtain agreement on the components of the NDA Re-Submission
	May 1	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	General Correspondence: EPIX submits a Type C Meeting Background Package for the June 5, 2008 Teleconference with the Division
	May 6	James Moore-FDA	Margaret Uprichard-EPIX	General Correspondence: EPIX submits 13 additional desk copies of the Type C Meeting Package for June 5, 2008 Teleconference
	June 30	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	NDA RESUBMISSION: EPIX Complete Response to the Approvable Letter of November 21, 2005, Pediatric Waiver Included
	August 14	R. Dwaine Rieves-FDA	Margaret Uprichard-EPIX	Confirmation of Tradename: EPIX is seeking Confirmation that VASOVIST is an acceptable proprietary tradename for gadofosveset trisodium

YEAR	DATE	TO	FROM	DESCRIPTION
2008	**October 3**	R. Dwaine Rieves-FDA	Margret Uprichard-EPIX	Response to Request for Information: EPIX's response to Division's September 23, 2008 fax requesting confirmation on the datasets provided in the NDA Resubmission and to the September 23, 2008 telephone call from Dr. James Moore requesting the address of the core imaging facility used for the MRI images.

VASOVIST NDA CORRESPONDENCE LOG

Date	To	From	Description
11/13/2003	Robert Morgan, EPIX	Jane Axelrad, FDA	Mail: FDA letter granting EPIX a requested small business waiver under section 736(d)(3)(B) of the Act
12/15/2003	Debra Suckney, EPIX	James Moore, FDA	Email: JM confirmed that EPIX should be able to pick up colored binders at the Central Document Room
12/24/2003	Debra Suckney, EPIX	James Moore, FDA	Email: JM confirmed with Dr. Mucci regarding data display sent via email. Dr. Mucci has not reviewed it yet, but will provide comments soon.
01/05/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Questions regarding eNDA Navigation Training/Request Information
01/07/2004	Debra Feldman, EPIX	James Moore, FDA	Email: Responded to questions put forth in 05 Jan 2004 email.
01/13/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Draft agenda and list of attendees for 15Jan2004 training on Navigation of eNDA
01/13/2004	Debra Feldman, EPIX	James Moore, FDA	Email: Request to utilize presentation attached to previous email in training
01/20/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Reminder to JM that Regulatory traveling to South America and to call cell phone if need arises. Requested FDA attendee list from 15Jan04 eNDA training session.
01/20/2004	Debra Feldman, EPIX	James Moore, FDA	Email: JM affirmed that he would fax attendee list 21Jan04
01/23/2004	Debra Feldman, EPIX	James Moore, FDA	Fax, FDA Letter: List of FDA attendees present at the 15Jan04 eNDA training session (13 total)
01/23/2004	Robert Morgan, EPIX	Patricia Stewart, FDA	FDA Letter: Official notification of receipt of NDA at FDA
01/29/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: VM left for James Moore regarding Standard Review priority Classification status per official letter. Moore called back on 01/30/04 w/ explanation.

Date	To	From	Description
02/02/2004	H.W. Ju, FDA	Debra Feldman, EPIX	Phone: DF responded to VM from Dr. Ju who requested information on clinical sites for phase 3 studies, safety and efficacy, design of blinded read trials
02/03/2004	H.W. Ju, FDA	Debra Feldman, EPIX	Phone: HWJ asked questions regarding efficacy parameters, blinded read, protocols, body regions studied, location of complete data set
02/04/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: Request to set up T-con with Christy John, Clinical Pharmacology Reviewer, to address his fatty meal question. T-con scheduled for 10am 02/05/04
02/04/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Dial-in instructions for 02/05/04 T-con
02/06/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Acknowledgement of action item initiated during T-con and approximate timing for response aimed for Feb 24 2004
02/10/2004	Dr. Hsein W. Ju, FDA	Robert Morgan, EPIX	Phone: RM followed-up on informational email regarding data FDA needed. Inquiry made regarding visit to BioImaging - explained that much of the data FDA will need to view is offsite and will take time to prepare.
02/13/2004	James Moore, FDA	Robert Morgan, EPIX	Phone: Confirmation that NDA 21-711 has been filed and under active review. Classification remains Standard with action date of Oct 15, 2004 but informed that this status may change and that, if so, it will be reflected in 74 Day Letter.
02/23/2004	James Moore, FDA	Debra Feldman, EPIX	Email: List of EPIX attendees from Feb 5, 2004 T-con with Christy John. Reaffirmed that EPIX will send analysis of plasma binding across studies in normal fasting and non-fasting subjects by end of week. Also will send copy of labeling from eNDA both in word and pdf formats

Date	To	From	Description
02/26/2004	Debra Feldman & Michelle Younis, EPIX	James Moore, FDA	Phone: Request for 3 additional copies of Vol 1 and 2 of NDA be marked 'Desk Copy' and sent directly to JM
02/27/2004	Robert Morgan, EPIX	Sally Loewke, FDA	Mail: FDA completed filing review and determined the EPIX application is sufficiently complete to permit a substantive review
03/02/2004	Robert Morgan, EPIX	Sally Loewke, FDA	Fax, FDA Letter: Filing review complete and Agency determination made that application of 02/13/04 sufficiently complete to permit a substantive review with potential review issues
03/10/2004	Debra Feldman, EPIX	James Moore, FDA	Phone: JM requested color copy of Vasovist label and name/address of Director of QA at BioImaging. EPIX confirmed receipt of 74 day letter.
03/11/2004	Roy Blay, FDA	Debra Feldman, EPIX	Phone: DF called RB since Dr. Ju will no longer be on the project. RB will take a look at the potential clinical sites for inspections and get back to EPIX soon.
03/11/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: Asked if he got emailed version of Vasovist label in color and if naming committee was reviewing label. JM said yes to both and that it was the naming committee who asked for it. Asked if EPIX should call Dr. Blay to exchange contact info. JM said yes.
03/11/2004	Dr. Ju, FDA	Debra Feldman, EPIX	Phone: Dr. Ju no longer on EPIX project. Dr. Roy Blay will take over. Will be contacted soon by Dr. Blay for a list of clinical sites for inspections
03/15/2004	Debra Feldman, EPIX	Roy Blay, FDA	Phone: Provided EPIX with a list of sites chosen for inspections. Also provided EPIX with a list of documents needed for the audit and other logistical issues were discussed.

Date	To	From	Description
03/17/2004	Debra Feldman, EPIX	Roy Blay, FDA	Phone: Dr. Blay said that FDA will only be inspecting Phase III Clinical sites. Also wanted CVs for PIs only. Monitors from CRO or EPIX may function as a translator as long as they didn't work directly w/ the study.
03/24/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Request for information from pharmacology reviewer regarding study of rodent model of drug-induced renal impairment
04/01/2004	Roy Blay, FDA	Debra Feldman, EPIX	Phone: DF asked FDA to give BioImaging advanced notice of inspection due to lengthy preparation time for bringing images to the workstations. Also, discussed materials being prepared for site inspections.
04/06/2004	Roy Blay, FDA	Debra Feldman, EPIX	Phone: Discussion regarding submission requirements for institutional read data to department of scientific investigations and logistics of audit at Dr. Wolff's site
04/16/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Request for information from clinical reviewer regarding EKG analysis for Studies MS-325-01A and 01C: QTc analysis as specified per FDA. Also, requested information regarding cardiac cycles that were used to calculate mean QT interval.
04/20/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Notification that 120 Day Safety Update sent 04/14/2004 as electronic submission
04/21/2004	Roy Blay, FDA	Debra Feldman, EPIX	Phone: Follow-up on Site audit package sent on 04/20/2004. Dr. Blay confirmed arrival. Questions posed re: potential timing. Dr. Blay outlined site audit procedures for both American and European sites. Note: contact log is incorrectly dated April 21, 2001. Correct year is 2004

Date	To	From	Description
04/23/2004	Robert Morgan, EPIX	James Moore, FDA	Phone: Michelle Younis answered call in Robert Morgan's absence. JM asked Michelle to relay information regarding the pre-IND package to RM
04/28/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: DF inquired into our status with naming committee. JM stated he had no update and they did not tolerate phone calls but expect mid-June notice. Question posed as to how many copies of 120-Day Safety update to send; JM responded one sufficient.
04/29/2004	Debra Feldman, EPIX	Roy Blay, FDA	Phone: Clarification of the section on protocols. RB requested updated direct telephone numbers for foreign sites
04/30/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA identified 10 syncopal events from AE datasets within NDA submission (3 labeled SAE and 2 summarized in ISS): need narratives in sufficient detail to assess severity to potential drug relationship; request detailed summary for each patient. Request to submit all electronically within 2 weeks
04/30/2004	Roy Blay, FDA	Debra Feldman, EPIX	Email: Provided direct telephone numbers for EPIX's three foreign sites selected for inspection
05/06/2004	Roy Blay, FDA	Debra Feldman, EPIX	Email: Follow up email pertaining to Dr. Wolff's address
05/17/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Notified FDA that the response to FDA request for Clinical Information #2 dated April 30, 2004 was submitted to the Agency on May 14, 2004
05/28/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Request clarification whether Ph 2/3 study protocols have specified critical threshold of 02 saturation at which appropriate medical interventions are required & list of medical interventions (if any) that were carried out in response to the drops

Date	To	From	Description
06/01/2004	Roy Blay, FDA	Debra Feldman, EPIX	Phone: DF asked RB regarding timing of foreign site inspections as sites had not received notification
06/15/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA requests re-evaluation of ECG ST segment depression data for 17 subjects
06/15/2004	Roy Blay, FDA	Debra Feldman, EPIX	Email: Notification that Dr. Edelman out of the office this week but contact information for his inspector obtained: Lisa Hayka ph 312-596-4259. DF requests call be put into her to ensure she is preparing for the MS-325-13 audit not MS-325-12 as mentioned in her message
06/18/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA request for statistical information regarding 1) primary analysis, 2) possible secondary analyses 3) secondary endpoints for determination of patient management
06/28/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA requests clarification on symbols (*, U or NA) used to relate stenosis level of categorical diagnoses
07/02/2004	James Moore, FDA	Debra Feldman, EPIX	Fax: List of attendees for Jun 30, 2004 T-con
07/02/2004	James Moore, FDA	Michelle Younis, EPIX	Email: Sent attendee list for Jun 30, 2004 T-con via email b/c FDA did not receive faxed copy
07/16/2004	James Moore, FDA	Robert Morgan, EPIX	Email: Notification of submission of Rat Renal Impairment study report
07/22/2004	James Moore, FDA	Debra Feldman, EPIX	Fax, FDA Letter: DMETS does not recommend use of proprietary name VASOVIST
07/23/2004	Debra Feldman, EPIX	Attila Kadar, FDA	Phone: Discussion centered around the best way to facilitate European Site Inspections. FDA provided EPIX an explanation of the process for setting up the site inspections in Europe. Provided EPIX with a list of things to do.

Date	To	From	Description
07/29/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Requests: Justification for selecting 2D-TOF as standard non-contrast MRA technique for all arterial regions, Avg effect analysis, different analytical strategy for handling of uninterpretable MRA images in primary data analysis, Vessel segment analysis, Subgroup analysis, Agreement between XRA readers, Aneurysms endpoint, Clarification regarding steady-state image.
08/03/2004	Debra Feldman, EPIX	Roy Blay, FDA	Phone: Requested individual data for AEs and vital signs for each of the 3 European clinical sites planned for inspection.
08/03/2004	Debra Feldman, EPIX	James Moore, FDA	Phone: JM wanted to coordinate a T-con with the FDA for 4Aug2004 to discuss: the location of the Phase III SAP's in the IND and Changes in the SAP from IND to NDA
08/04/2004	Debra Feldman, EPIX	James Moore, FDA	Phone: GM requested response to 2 questions: 1) Where is the stat analysis plan for four pivotal trials located in the IND for MS-325? 2) Were there any changes to the stat analysis plan from the IND to the NDA?
08/06/2004	Attila Kadar, FDA	Debra Feldman, EPIX	Email: DF able to confirm consecutive dates for our clinical site inspections for Dr. Thurnher, Dr. Neuwirth, Dr. Vymazal
08/10/2004	James Moore, FDA	Debra Feldman, EPIX	Email: EPIX confirmed T-con for 8-11-2004 with Dial in Number
08/11/2004	EPIX	FDA	Phone: T-con to discuss the Phase III image data and the availability of this data for FDA review; meeting minutes
08/11/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Confirming 12Aug2004 T-con at 11am. Provided dial-in number.

Date	To	From	Description
08/12/2004	George Mills, FDA	Steve Einstein, BioImaging	Phone: Questions regarding imaging issues, if FDA needed BioImaging Database, what is the scope of the submission, hardware requirements, etc.
08/12/2004	EPIX	FDA	Phone: T-con with BioImaging and FDA to discuss the potential for FDA to review the Phase 3 imaging data at their core imaging laboratory. EPIX to submit plan for the transfer and review of images at FDA.
08/13/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA request for statistical information regarding Study MS-325-14 and MS-325-15
08/13/2004	EPIX	FDA	Phone: T-con regarding FDA's fax dated Aug 13, 2004 – request for statistical information re. vessel-weighted stats analysis for MS-325-14
08/18/2004	Attila Kadar, FDA	Debra Feldman, EPIX	Email: Confirmation for Site Inspections in Europe including EPIX representative, Site No./location and Hotel information
08/18/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA Request for statistical information – EPIX to provide two-sided 95% CI for Sensitivity, Specificity for readers in all four studies
08/18/2004	EPIX	FDA	Phone: Discussion with Dr. Mucci regarding the organization of the efficacy database
08/18/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Confirm T-con in a few minutes. Provided dial in number.
08/19/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA request for several additional post-approval stability commitments
08/19/2004	Debra Feldman, EPIX	James Moore, FDA	Phone: JM said that he doesn't feel that a T-con is necessary if EPIX understands the CMC requests in the FDA Fax dated 19Aug2004.
08/23/2004	Attila Kadar, FDA	Robert Morgan, EPIX	Email: Information regarding site inspections in Europe including Vienna Hotel Information

Date	To	From	Description
08/24/2004	George Mills, FDA	Robert Morgan, EPIX	Phone: RM called GM to give him an update on timeline for training FDA and GE Workstations and blinded reads. Sept. 2 is the proposed date. GM to confirm w/ staff.
08/24/2004	George Mills, FDA	Robert Morgan, EPIX	Email: EPIX proposes Sept. 2, 2004 as the date for EPIX/BioImaging visit FDA to install the GE Workstation
08/25/2004	George Mills, FDA	Robert Morgan, EPIX	Email: Notification that Larry Schwartz is available for the proposed Sept. 2 image training session at FDA. Question as to whether the proposed date is acceptable to FDA.
08/25/2004	Robert Morgan, EPIX	George Mills, FDA	Email: GM stated that Sept. 2 is acceptable for EPIX to conduct image training session at FDA. GM would like to know when Dr. Schwartz will be in WOC 2 for the training and orientation.
08/25/2004	George Mills, FDA	Robert Morgan, EPIX	Email: Proposed a plan for the FDA training. Will send FDA a list of attendees. Will bring 6 copies of the binders containing the CRFs that correspond to the images to be presented.
08/25/2004	George Mills, FDA	Robert Morgan, EPIX	Email: Availability of Dr. Larry Schwartz to participate in the proposed training date of 09/02/2004.
08/26/2004	James Moore, FDA	Debra Feldman, EPIX	Fax: Response to voicemail request dated August 25, 2004. Provided list of T-cons taken place between FDA and EPIX regarding NDA beginning 1 Jun 04 to present.
08/30/2004	Debra Feldman, EPIX	Roy Blay, FDA	Phone: FDA called to confirm BioImaging address/contact information. FDA assured EPIX that a 2-3 day warning will be given before FDA goes to BioImaging to Audit.

Date	To	From	Description
08/30/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA's EDR requests resubmission of 19Aug2004 submission (response to request for information received on 29July2004). MS Word and .csv files not accepted.
08/30/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Request for information from pharmacology reviewer regarding Zinc and Zinc Fosveset levels in moderate and severe renal impaired patients.
08/31/2004	Roy Blay, FDA	Debra Feldman/Robert Morgan, EPIX	Phone: Discussion on scope of Dr. Blay's inspection of BioImaging, shortage of machines at BioImaging. Also, not all images can be available on this machine. BioImaging requests specific sites and pt numbers in advance to prep for audit.
08/31/2004	James Moore, FDA	Debra Feldman, EPIX	Email: List of EPIX attendees to go down to FDA for blinded read training on Thursday Sept 2, 2004
09/02/2004	George Mills, FDA	Robert Morgan, EPIX	Email: Follow-up email to earlier discussion with GM regarding tradename recommendation reconsideration. RM requests input from GM as to whether FDA will reconsider DMETS recommendation based on the data from the naming study comparing Vasovist to Magnevist
09/02/2004	Detlev Pfefferer, Schering	Robert Morgan, EPIX	Phone: Overview of conversation w/ Dr. Mills regarding EPIX's request for reconsideration of DMETS recommendation for VASOVIST. RM commits to sending GM copy of 20Aug2004 submission via email.

Date	To	From	Description
09/03/2004	George Mills, FDA	Robert Morgan, EPIX	Phone: Discussion regarding name challenge for Vasovist. GM stated no decision has been made yet but does not know where in the process the naming consideration is. GM recommends starting proposed study comparing Vasovist and Magnevist.
09/03/2004	Debra Feldman, EPIX	Thuy Nguyen, FDA	Fax: FDA requests location of documentation in NDA of the minimum performance of MS-325 MRA and the size of the performance improvement of MS-325 MRA over non-contrast MRA in terms of sensitivity and specificity that were prospectively defined in the four phase 3 protocols
09/09/2004	James Moore, FDA	Robert Morgan, EPIX	Phone: Follow-up to earlier call w/ FDA regarding name change for VASOVIST – regarding our request for FDA to re-consider their recommendations
09/13/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA request for information on why sample sizes are different for Study #12 and Study #13 when they have identical designs.
09/20/2004	James Moore, FDA	Debra Feldman, EPIX	Fax: Per JM request, provided list of t-cons between FDA/EPIX occurring 01June 2004 – present (26Aug2004)
09/23/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: DF called JM to touch base on status of NDA review
10/01/2004	Debra Feldman, EPIX	James Moore, FDA	Fax, FDA Letter: FDA letter stating extension of NDA review date by 90 days due to submission of major amendment within 3 months of user fee goal date
10/05/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: List of attendees who will be present on 7Oct2004 T-con
10/06/2004	James Moore, FDA	Robert Morgan, EPIX	Email: Conf call-in # and list of EPIX attendees on 7Oct2004 T-con

Date	To	From	Description
10/07/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA statistician unable to reproduce results from data in new data set (supplementary database Aug31MS325Supp_data2-includes flats for uninterpretables). Asked EPIX to investigate problem
10/07/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: Per a discussion during the 7Oct2004 T-con, FDA provided a list of 34 pts who have experienced an acute hemoglobin drop of 2 grams or more within 72 hours post-dosing. EPIX to provide response to questions posed during the T-con
10/12/2004	Dr. Mucci, FDA	Robert Morgan, EPIX	Email: Recalculated values for sens, spec and accuracy
10/14/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA requests individual data for Report No. A10333 (pre-clinical study report).
10/18/2004	Anthony Mucci, FDA	Robert Morgan/ Robert Weisskoff, EPIX	Phone: EPIX called FDA to follow-up on 12Oct2005 submission (statistics questions).
10/19/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: DF called JM to confirm receipt of EPIX's meeting minutes & to inform him of upcoming submissions based on action items from 7Oct2004 T-con
10/20/2004	Anthony Mucci, FDA	Robert Morgan/Robert Weisskoff, EPIX	Phone: Discussion on some of AM's preliminary analysis. Compared AM's results w/ EPIX's.
10/20/2004	Anthony Mucci, FDA	Robert Weisskoff, EPIX	Email: Discussion on difference in sensitivity Post-Pre between the "restricted" data set & the "extrapolated."
10/25/2004	James Moore, FDA	Debra Feldman, EPIX	Email: DF let JM know that Robert Morgan is dropping off 22Oct2004 submission in person
10/27/2004	Robert Morgan/Robert Weisskoff, EPIX	Anthony Mucci, FDA	Phone: AM needed help in finding the analyses in 22Oct2004 submission
11/03/2004	James Moore, FDA	Debra Feldman, EPIX	Email: JM wanted to know when response to clinical request of 29Jul2004 was submitted. DF: it was submitted on 12Aug2004

Date	To	From	Description
11/03/2004	Debra Feldman, EPIX	CDER, FDA	Fax: FDA wants re-submission of individual data for A10333. Original submission CD arrived broken at FDA.
11/03/2004	Robert Weisskoff, EPIX	Anthony Mucci, FDA	Phone: AM called to see if EPIX had a specific analysis (different method of averaging than what was used in NDA and FDA responses). Also discussed discrepancy between EPIX's calculations and FDA calculations for Study 14.
11/04/2004	George Mills, FDA	Andrew Uprichard/Robert Morgan, EPIX	Phone: GM still concerned with the asymmetry of # of uninterpretable scans from baseline. Review team at FDA will discuss in the next week or so. AU (EPIX) introduced himself and asked if EPIX can do anything to aid in the review and asked about potential Ph. IV commitment. GM didn't volunteer any information on that.
11/09/2004	James Moore, FDA	Debra Feldman, EPIX	Phone: JM stated that DMETS returned with same recommendation regarding Vasovist
11/10/2004	George Mills, FDA	Robert Morgan, EPIX	Email: EPIX request an informal meeting to discuss on-going NDA review. EPIX learned of DMETS recommendation on Vasovist – no change.
11/11/2004	Robert Morgan, EPIX	George Mills, FDA	Email: FDA responds to EPIX request for informal meeting
11/17/2004	Robert Morgan, EPIX	Anthony Mucci, FDA	Phone: Discussion regarding % stenosis recorded for studies 12 and 13
11/23/2004	Robert Morgan, EPIX	Anthony Mucci, FDA	Phone: AM needed help in locating the original dataset in eNDA
12/01/2004	Debra Feldman, EPIX	James Moore and George Mills, FDA	Phone: Request from GM to schedule T-con with EPIX to discuss the NDA review

Date	To	From	Description
12/03/2004	George Mills, FDA	Robert Morgan, EPIX	Email: RM requests adding a brief discussion of the Trade Name for MS-325 on T-con agenda
12/06/2004	James Moore, FDA	Debra Feldman, EPIX	Email: Provided dial-in number for Dec 7, 2004 T-con
12/06/2004	Debra Feldman, EPIX	James Moore, FDA	Email: JM confirmed that he will call in to the T-con scheduled for 7Dec2004 at the number provided by EPIX
12/10/2004	Mike Webb, EPIX	Julie Beitz, FDA	Phone: Discussion on statistics and planning a face to face meeting before action letter is issued
12/10/2004	George Mills, Florence Houn, FDA	Andrew Uprichard, Mike Webb, EPIX	Phone: AU called GM to let him know that EPIX disagrees with FDA's approach to MS-325. EPIX plans to call FH and ask for a meeting. MW calls FH and leaves a voicemail stating that FDA has given EPIX discordant advice and that NDA should be approved on the basis of existing data, not new studies.
12/15/2004	Robert Morgan, EPIX	Anthony Mucci, FDA	Email: Discussion on appropriateness of imputation scheme, alternative statistics, 95% CI, scheduling a T-con to discuss these issues in detail
12/16/2004	Anthony Mucci, FDA	Robert Weiskoff, Andrew Uprichard, Robert Morgan, EPIX	Phone: Discussion w/ FDA regarding ways to combine data that will give an acceptable statistic that shows improvement for Vasovist. 3 Action items for EPIX
12/17/2004	Debra Feldman, EPIX	James Moore, FDA	Fax: List of attendees at the EPIX/FDA meeting at FDA on 13Dec2004
01/03/2005	James Moore, FDA	Robert Morgan, EPIX	Email: RM asks if FDA received EPIX submissions dated 29Dec2004 (Clinical Pharmacology and Efficacy 7).
01/03/2005	Robert Morgan, EPIX	James Moore, FDA	Email: JM responds to TM's email that he didn't see the 29Dec2004 submissions, but will check with Dr. Mills

Date	To	From	Description
01/05/2005	Nancy Buc, Consultant	Andrew Uprichard, EPIX	Phone: AU called NB, who had just had a discussion with Julie Beitz at FDA. JB said that EPIX will get a letter on the action date. NB suggested that EPIX should not contact FDA at the moment.
01/12/2005	Robert Morgan, EPIX	Julie Beitz, FDA	Fax, FDA Letter: Approvable letter from FDA for Vasovist. Need to address several clinical deficiencies before product can be approved and marketed.
01/14/2005	James Moore, FDA	Robert Morgan, EPIX	Email: RM requests clarification on whether Vasovist is acceptable tradename for MS-325 since it is used throughout the action (Approvable) letter.
01/19/2005	James Moore, FDA	Debra Feldman, EPIX	Email: DF emailed cover letter/ 356h to JM – letter of intent to amend NDA21-711 sent on 18Jan2005
04/26/2005	Patricia Stewart, FDA	Robert Morgan, EPIX	Email: Requested name of new PM since Capt. Moore has retired
04/27/2005	Kaye Kang, FDA	Robert Morgan, EPIX	Email: Reminder to FDA that EPIX needs new PM for both MS-325 and EP-2104R
04/27/2005	Robert Morgan, EPIX	Kaye Kang, FDA	Email: FDA will get back to EPIX newly assigned PM
05/05/2005	Robert Morgan, EPIX	Kaye Kang, FDA	Phone: New FDA PM for EPIX is Thuy Nguyen – EPIX has worked with her previously. KK confirmed that FDA 'reorg' will occur in July. Also some discussion of the final structure of the division after the re-org.
05/26/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Phone: TN confirmed that FDA did receive Complete Response submission dated May 23, 2005 and it has been distributed to review team. Also, James Moore might be coming back as EPIX PM as a civilian.
06/06/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Phone: RM called TN to see if Complete Response has been accepted. Left voice mail and requested TN to call back.

Date	To	From	Description
06/08/2005	Robert Morgan, EPIX	Thuy Nguyen, FDA	Phone: TN returned RM's call and said that she needed 4 more copies of Complete Response (Volume 1 of Part 1 only) to be sent to FDA. There was also some discussion on FDA's action date and that it was not according to the MAPP on the FDA website.
06/14/2005	Julie Beitz, FDA	Nancy Buc, EPIX Counsel	Phone: Conversation regarding timing of FDA reorganization and EPIX re-submission (Complete Response to Approvable Letter). JB mentioned that George Mills has ideas on how to move this NDA forward.
06/15/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Phone: Discussed scheduling of t-con for June 23, 2005 to discuss EPIX re-submission (Complete Response). TN would not confirm if FDA believed re-submission is considered a Complete Response. This is to be discussed during the t-con.
06/16/2005	Thuy Nguyen, FDA	Debra Feldman, EPIX	Phone: Conversation to confirm that TN will be sending the list of attendees for FDA/EPIX t-con scheduled for 23June2005.
06/16/2005	Robert Morgan, EPIX	Thuy Nguyen, FDA	Fax: TN sent list of FDA attendees for 23June2005 T-Con.
06/17/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Fax: RM requested that FDA clarify the purpose of the 23Jun2005 t-con. Also, requested confirmation that FDA will notify EPIX in writing whether EPIX May23, 2005 re-submission is a complete response in accordance with MAPP 6020.4
06/17/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Email: RM wanted confirmation that TN received EPIX fax
06/21/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Email: RM wanted to confirm again that TN received EPIX fax of 17Jun2005
06/22/2005	Thuy Nguyen, FDA	Debra Feldman, EPIX	Fax: DF sent dial-in instructions for EPIX/FDA 23Jun2005 t-con

Date	To	From	Description
06/23/2005	Thuy Nguyen, FDA	Robert Morgan, EPIX	Fax: RM sent list of EPIX attendees for 23Jun2005 t-con
06/29/2005	Robert Morgan, EPIX	Thuy Nguyen, FDA	Fax: Official FDA meeting minutes for 23Jun2005 t-con to discuss NDA Complete Response submission. Includes attendees and action items.
06/30/2005	Robert Morgan, EPIX	Thuy Nguyen, FDA	Phone: TN stated that the PDUFA date for 23May2005 EPIX Complete Response is 23Nov2005 (6 month review period).
07/26/2005	Robert Morgan, EPIX	Kyong Kang, FDA	Mail: FDA denial for EPIX 13Jul2005 request for meeting to discuss ph IV plan. Letter is dated 7/26/05, but wasn't received until 8/2/05.
07/29/2005	Karen Weiss, FDA	Nancy Buc, EPIX	Mail: Sent key documents (29Dec2005 submission, Approvable letter, Complete response) to Karen Weiss, who will most likely be supervising George Mills.
08/01/2005	Andrew Uprichard, EPIX	Nancy Buc	Email: Confirmation of information sent to FDA by Nancy Buc
08/09/2005	Debra Feldman, EPIX	Thuy Nguyen, FDA	Phone: TN called to say that James Moore will be returning as EPIX project manager, but this time as a civilian.
08/10/2005	Debra Feldman, EPIX	James Moore, FDA	Phone: JM left DF a voice mail saying that FDA will be sending a fax shortly with statistical questions
08/10/2005	Debra Feldman, EPIX	James Moore, FDA	Fax: FDA requested breakdown of uninterpretable rates and BR rates for each reader by study and site; a restricted data set with variables provided only; request for clarification on items in Complete Response
08/15/2005	Debra Feldman, EPIX	James Moore, FDA	Phone: JM agreed to let EPIX have an extension in responding to FDA fax dated 10Aug2005

Date	To	From	Description
08/24/2005	Debra Feldman, EPIX	James Moore, FDA	Fax: Pharm/Tox question on Schering Report A25681 (P450 enzyme inhibition study) – requested positive and negative control data
09/13/2005	James Moore, FDA	Robert Morgan, EPIX	Email: RM requests t-con w/ FDA to discuss any pending issue w/ NDA complete response review
09/13/2005	Robert Morgan, EPIX	James Moore, FDA	Email: Requested additional information with regards to proposed t-con agenda
09/13/2005	Robert Morgan, EPIX	James Moore, FDA	Email: JM requested more detailed information for proposed t-con agenda
09/13/2005	James Moore, FDA	Robert Morgan, EPIX	Email: RM sent a more detailed agenda for the proposed t-con
09/20/2005	Michael Astrue, EPIX	George Mills, FDA	Phone: Discussion w/ GM regarding request for a face-to-face mtg to discuss the options available to EPIX on its pending application
09/22/2005	Mike Astrue, EPIX	George Mills, FDA	Phone: Discussion regarding proposed t-con with FDA to discuss issues, EPIX considering requesting Advisory Committee meeting, and time considerations for a re-read of pivotal trial imaging data
10/04/2005	Debra Feldman, EPIX	James Moore, FDA	Fax: Request for additional information on Nonclinical study report A25681 – individual data expressed as turnover rate and inhibition %
10/04/2005	Debra Feldman, EPIX	James Moore, FDA.	Phone: JM left DF a voicemail message that he will be faxing an FDA request for additional information on non-clinical study A25681
10/13/2005	George Mills, FDA	Michael Astrue, EPIX	Phone: Candid discussion on NDA review, EPIX intent to request advisory committee, EPIX inability to have open discussions with FDA

Date	To	From	Description
10/21/2005	Richard Pazdur, FDA	Michael Astrue, EPIX	Phone: Conference Call Minutes - MA outlined reasons why Vasovist should be approved. RP had different ideas on how to move forward with NDA review and stated that if issues outlined in Approvable letter weren't answered in the complete response, then we know what to expect at the end of Nov 2005
11/21/2005	Robert Morgan, EPIX	Karen Weiss, FDA	Mail: FDA receipt approvable letter of NDA with additional request for data before application can be approved
11/22/2005	Debra Feldman, EPIX	James Moore, FDA	Fax, FDA letter: CR lacked data requested in Jan2005 Approvable letter. FDA requests data from new studies, safety update and updated draft labeling
12/01/2005	James Moore, FDA	Robert Morgan, EPIX	Email: RM wrote JM to ask if it's acceptable to fax in the 10-day response to approvable letter. JM responded that it would be ok to fax it.
12/01/2005	James Moore, FDA	Debra Feldman, EPIX	Email: DF wrote to JM stating she would be faxing in the 10-day response to Approvable letter shortly and requested confirmation of receipt. JM confirmed receipt of the fax.
12/05/2005	James Moore, FDA	Debra Feldman, EPIX	Email: DF emailed JM stating that she would be faxing in Meeting Request and requested confirmation upon receipt.
12/05/2005	Debra Feldman, EPIX	James Moore, FDA	Email: JM responded that he will let DF know when he receives EPIX meeting request fax
12/06/2005	James Moore, FDA	Debra Feldman, EPIX	Phone: DF called to confirm FDA receipt of EPIX Type A meeting request

Date	To	From	Description
12/12/2005	Debra Feldman, EPIX	James Moore, FDA	Fax, FDA Letter: Type A meeting request granted with FDA on January 5, 2006 at 1pm. FDA requested background information to be submitted at least two weeks prior to the meeting date.
01/03/2006	Debra Feldman, EPIX	James Moore, FDA	Phone: JM called DF to say that Dr. Mills will not be presenting at the 05Jan06 mtg and that EPIX should send a revised agenda to reflect this change.
01/03/2006	James Moore, FDA	Debra Feldman, EPIX	Fax: 05Jan2006 Meeting Agenda
01/04/2006	Debra Feldman, EPIX	James Moore, FDA	Fax: Comments from FDA on EPIX 05Jan06 meeting package – on design of new clinical trials and blinded read.
01/04/2006	James Moore, FDA	Robert Morgan, EPIX	Phone: RM called JM to confirm receipt of revised agenda for 05Jan06 mtg and to see if FDA will be sending responses to EPIX questions put forth in the briefing package. JM responded that he will be faxing over FDA responses soon. JM called later on to confirm EPIX had received FDA fax. RM confirmed.
01/04/2006	James Moore, FDA	Robert Morgan, EPIX	Email: RM contacted JM to state that EPIX will be making an informal presentation without slides at the 05Jan2006 meeting
01/04/2006	James Moore, FDA	Robert Morgan, EPIX	Email: RM informed JM of a slight change in attendee list due to the reduction in regulatory staff at EPIX – Nancy Buc will attend the meeting
01/05/2006	James Moore, FDA	Robert Morgan, EPIX	Email: RM emailed JM to return his call. JM emailed stating that adding Nancy Buc to the attendee list would not be a problem
01/09/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: AS informed JM of a change in regulatory staff at EPIX and stated that she will be the main point of contact at EPIX

Date	To	From	Description
02/02/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: AS called JM to introduce herself as new point of contact at EPIX. Also – called to inform him that she's faxing a meeting request to FDA and would like confirmation of receipt. JM called back to confirm receipt of fax
02/03/2006	Aarati Sridharan, EPIX	Kaye Kang, FDA	Phone: KK called AS to discuss the meeting request sent on 2Feb2006. AS stated that she'd call back in a few minutes after gathering the EPIX team.
02/03/2006	Kaye Kang, FDA	Aarati Sridharan, EPIX	Phone: AS called KK after gathering the EPIX team. George Mills stated that he wants to see the SAP along with a protocol in the meeting package. He feels that this would be the most productive use of meeting time
02/03/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: JM called AS to say that he will be faxing mtg minutes from the 05Jan2006 mtg
02/03/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: Meeting minutes from 05Jan2006 meeting where EPIX/FDA discussed how the Vasovist program should proceed (design of new clinical trials/ blinded reads, etc.)
02/06/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: AS called JM to see if a date for the mtg request sent the previous week had been determined. JM stated that it would most likely be on April 5, 2006.
02/07/2006	Aarati Sridharan, EPIX	James Moore, FDA	FDA Letter: Granting EPIX a Type B meeting date for April 5, 2006 to discuss a draft clinical protocol
03/01/2006	George Mills, FDA	Andrew Uprichard, EPIX	Phone: AU called GM to request postponing the scheduled 05Apr2006 meeting by 2 or 3 days to ensure presence of key consultants

Date	To	From	Description
03/02/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: AS called JM to ask when a good time would be on March 3, 2006 to come by and deliver the desk copies of the information package for the 05Apr2006 mtg
03/06/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: Two conversations: JM called to request a list of questions to go along with the information package for the April meeting. He also asked to have a teleconference with EPIX.
03/07/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: AS emailed JM to state that EPIX would submit list of questions later on in the week. AS also proposed alternative dates for the proposed teleconference.
03/08/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: Multiple conversations regarding the date of the FDA proposed T-con to discuss the date of the meeting
03/08/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: JM called AS to state that he had just faxed a response to EPIX's request to amend the meeting minutes from the 05Jan2006 meeting.
03/08/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: Response to EPIX's request to clarify and change certain points in the FDA meeting minutes from the January 5, 2006 meeting
03/08/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: AS emailed JM with the t-con dial-in details
03/10/2006	James Moore, FDA	Aarati Sridharan, EPIX	Fax: Requested List of Questions for April 5, 2007 meeting
03/10/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: AS called JM to let him know that the list of questions for the April meeting had been submitted
03/10/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: FDA requested revision on page 37 (SN219) of the IB
03/13/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: Two contact logs finalizing the date and time of t-con with FDA
03/14/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: Two additional contact logs regarding minor changes to t-con date/time

Date	To	From	Description
03/16/2006	George Mills, FDA	Aarati Sridharan, EPIX	Phone: Discussion (T-con) with FDA with regard to postponing the April 5th meeting and extending the meeting to 2 hours in order to fully discuss the list of questions submitted
03/28/2006	Aarati Sridharan, EPIX	James Moore, FDA	Phone: Two conversations regarding the list of attendees for the April 5th meeting
03/29/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: Revised list of attendees for the April 5th meeting
03/31/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: JM faxed a response to EPIX's list of questions and provided clarity on the proposed clinical trial/SAP/Reader Training Manual included in the Briefing Package
04/03/2006	James Moore, FDA	Aarati Sridharan, EPIX	Email: Agenda for the meeting on April 5th
05/03/2006	James Moore, FDA	Aarati Sridharan, EPIX	Phone: Call to request FDA meeting minutes from Apr 5th meeting
05/05/2006	Aarati Sridharan, EPIX	James Moore, FDA	Fax: Meeting minutes from April 5, 2006
05/18/2006	Aarati Sridharan, EPIX	Grace Carmouze, EPIX	Phone: Division called to confirm receipt of submission. Division will call back with a conference call time
05/25/2006	Andrew Uprichard, EPIX	George Mills, FDA	Phone: Requested that EPIX investigate occurrence of NSF and NFD with Vasovist
06/01/2006	James Moore, FDA	Aarati Sridharan, EPIX	Fax: Review of safety database for NFD as requested
07/07/2006	Nancy Buc, EPIX	Kim Colangelo, FDA	Fax: Appeal has been forwarded to John Jenkins, OND, CDER for review
08/25/2006	Andrew Uprichard, Phillip Graham, EPIX	John Jenkins, FDA	Fax, FDA Letter: Appeal is denied. Jenkins concurs w/ the regulatory standards imposed by ODE III and OODP in their reviews of this NDA
10/12/2006	Aarati Sridharan, EPIX	Kim Colangelo, FDA	Fax, Mail: Granted meeting w/ FDA on 07Nov2006

Date	To	From	Description
10/13/2006	George Mills, Louis Marzella, Kyong Kang, FDA	Mike Astrue, Andrew Uprichard, EPIX	Phone: Conversation between FDA and EPIX regarding: PDUFA target date, formal meetings in advance, advisory committees.
10/31/2006	Nicol Gross, FDA	Aarati Sridharan, EPIX	Email: List of EPIX attendees for 07Nov2006 meeting
11/01/2006	Nicol Gross, FDA	Aarati Sridharan, EPIX	Email: Revised list of EPIX attendees for Nov. 7, 2006 meeting
11/09/2006	Nancy Buc, EPIX	Kim Colangelo, FDA	Fax: List of FDA attendees at the 07Nov2006 meeting and request for slides presented
11/14/2006	Kim Colangelo, FDA	Nancy Buc, EPIX	Email: Sent KC a copy of slides used at the Nov. 7, 2006 meeting
12/15/2006	Aarati Sridharan, EPIX	Kim Colangelo, FDA	Fax: Post-Formal Dispute Resolution meeting minutes from Nov 7, 2006
12/19/2006	Aarati Sridharan, EPIX	Kim Colangelo, FDA	Fax: FDA Signature page for 12/11/2006
03/29/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Fax, Mail: Letter stating that meeting request has been granted. Meeting date set for May 8, 2007.
05/02/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Email: List of attendees for the May 8, 2007 meeting with CDER/ Dr. Throckmorton
05/03/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Email: Revised list of attendees to include Harold Goldstein
05/03/2007	Aarati Sridharan, EPIX	Melanie Blank, FDA	Email, Phone: Requests clarification on information presented in the Feb. 27th Appeal to CDER. EPIX informs Dr. Blank that we would provide responses to any questions from the Division, Dr. Throckmorton after the meeting.
05/07/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Email: FDA would like to discuss these two items at the meeting: Conduct of clinical trials and advisory committee meeting.
05/08/2007	FDA	EPIX	Appeal of Approvable Letter - Meeting with CDER (Dr. Throckmorton). Not submitted to the NDA.
05/09/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Email: List of attendees at May 8, 2007 meeting at FDA

Date	To	From	Description
05/15/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Phone: GC requests responses to questions asked at May 8th meeting. AS informs GC that the submission is on its way.
05/15/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Phone: EPIX will submit a response to the questions from May 8th meeting on May 17th
05/17/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Phone: Left voice mail that EPIX submitted a response to May 8th questions. Requested confirmation of receipt
05/18/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Phone: Received the May 17th submission. EPIX requested Dr. Throckmorton's direct phone number
05/21/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Email, Phone: Emails and phone calls to determine date for teleconference w/ Dr. Throckmorton and dial-in details
05/23/2007	Doug Throckmorton, FDA	Andrew Uprichard, EPIX	Phone: Follow-up to May 8th meeting. DT provided an update on the status of review. AU stated that EPIX is available to help in any way.
05/31/2007	Grace Carmouze, FDA	Aarati Sridharan, EPIX	Email: Slides from May 8th meeting w/ FDA
05/31/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Phone: GC called to request a copy of the slides used at the May 31, 2007. She also asks to schedule a tcon w/ Dr. Uprichard b/c Dr. Throckmorton has a few questions he'd like to discuss with regard to the between-reader variability seen in the scans.
06/04/2007	Doug Throckmorton/ Grace Carmouze, FDA	Andrew Uprichard, EPIX	Email: Follow-up to June 1st t-con at which Dr. Mucci raised questions on concordance of blinded readers in calling vessel segments uninterpretable
06/06/2007	Grace Carmouze, FDA	Margaret Uprichard, EPIX	Phone: MU called GC to follow up on June 4th submission and asked if they needed additional information. GC indicated that Dr. Throckmorton had what he needed.

Date	To	From	Description
06/07/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Fax: Formal Dispute Resolution Meeting minutes (Chaired by Dr. Throckmorton) from May 8, 2007
06/14/2007	Aarati Sridharan, EPIX	Grace Carmouze, FDA	Phone: FDA called with regards to clarifying location of document within the Appeal
06/15/2007	Maggie Uprichard, EPIX	Grace Carmouze, FDA	Fax, FDA Letter: Dr. Throckmorton's Decision regarding EPIX Appeal of the approvable letters: two new clinical studies no longer needed, blinded re-read of data is sufficient
07/02/2007	FDA	EPIX	Mail: Meeting minutes (Discussion in follow-up to the June 15, 2007 letter from Dr. Douglas Throckmorton)
07/20/2007	Margaret Uprichard, EPIX	Douglas Throckmorton, FDA	Mail: EPIX Initial Request letter to FDA for clarification of two points with regard to NSF & Pre-specified analysis dated 19June2007, FDA response letter dated 15June2007. FDA reiterating the points with their response
08/29/2007	James Moore, FDA	Maggie Uprichard, EPIX	Phone: MU leaves two voice messages for JM to try to schedule a meeting date to discuss the Vasovist Re-Read
09/07/2007	James Moore, FDA	Margaret Uprichard, EPIX	Phone: Discussed scheduling the Type A meeting to discuss re-read protocol and associated materials submitted on August 23, 2007
09/11/2007	James Moore & Grace Carmouze, FDA	Margaret Uprichard, EPIX	Phone: Called Dr. Moore to discuss scheduling of the Type A meeting (meeting request submitted 8/30/2007) to discuss the re-read protocol and associated materials submitted on August 23, 2007
09/13/2007	James Moore, FDA	Margaret Uprichard, EPIX	Phone: Meeting scheduled for October 23, 2007
09/13/2007	Margaret Uprichard, EPIX	James Moore, FDA	FDA Letter, Mail: Letter granting Type B meeting on Oct 23, 2007 to discuss Vasovist Re-read

Date	To	From	Description
09/25/2007	James Moore, FDA	Margaret Uprichard, EPIX	Mail: Response to request for additional desk copies of August 23 submission
10/10/2007	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Preliminary responses from FDA requesting additional information regarding Meeting Package dated August 23, 2007
10/10/2007	James Moore, FDA	Margaret Uprichard, EPIX	Email: Confirmed T-con for Oct 11 with attached Re-read glossary information
10/11/2007	FDA	EPIX	Mail: Meeting minutes – Discussion regarding comments/ questions received from the new medical review team. Primarily involving "Clarification of Terms"
10/15/2007	James Moore, FDA	Margaret Uprichard, EPIX	Fax: EPIX response to October 10, 2007 faxed questions on Vasovist Re-read protocol
10/22/2007	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Clinical/statistical comments on August 23, 2007 Meeting Package (which contained blinded re-read materials)
10/26/2007	Kyong Kang & Grace Carmouze, FDA	Margaret Uprichard, EPIX	Email: A copy of meeting minutes forwarded to Kyong Kang and Grace Carmouze to ensure timely distribution. Also a complaint is issued with regards to Dr. Moore's lack of urgency and Follow up skills.
10/30/2007	Margaret Uprichard, EPIX	James Moore, FDA	Fax: FDA draft comments in further follow-up to the meeting held on 10/23/2007
10/30/2007	Margaret Uprichard, EPIX	James Moore, FDA	Email: A list of FDA Division participants for 10/30/2007 T-Con
11/07/2007	James Moore, FDA	Shahidah Muhammad, EPIX	Phone: Voicemail left for JM regarding refax of 30Oct2007 minutes
11/07/2007	James Moore, FDA	Margaret Uprichard, EPIX	Fax: EPIX meeting minutes from the 10/30/2007 T-con
11/21/2007	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Meeting minutes from Tuesday, October 23, 2007 meeting

Date	To	From	Description
12/05/2007	James Moore, FDA	Margaret Uprichard, EPIX	Email: Status inquiry of November 14, 2007 submission for the re-read of images from Vasovist phase 3 studies
12/13/2007	James Moore, FDA	Margaret Uprichard, EPIX	Email: T-con scheduled for December 20, 2007 Dial-in number included
12/19/2007	Margaret Uprichard, EPIX	James Moore, FDA	Fax: A list of topics and comments to be discussed during scheduled T-con on December 20, 2007
01/22/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: FDA Fax of Correction McNemar's Equation
01/22/2008	Grace Carmouze & Kyong Kang, FDA	Margaret Uprichard, EPIX	Email: Request confirmation regarding the Appropriate Regulatory Mechanism for review of the December 21, 2007 T-con
01/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Changes to the statistical analysis plan for the Basovist re-read protocol as requested
01/31/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax, Mail: Agency's response to December 21, 2007 Submission for NDA 21-711
01/31/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Request for clarification on the Division's classification of the re-submission in response to Action Letters w/ reference being made to the Agency's Action Letter Fax of January 29, 2008
01/31/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Reference is being made to the division's Action Letter of January 29, 2008. The division's response to EPIX request clarifying that the re-submission will be classified w/ reference to the Final blinded re-read of 12.21.2007.
04/03/2008	R. Dwaine Rieves, FDA	Margaret Uprichard, EPIX	Fax: Request for teleconference to discuss NDA Resubmission
04/16/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: T-con scheduled for June 5, 2008 to discuss NDA resubmission with questions from EPIX with regard to the Division's NDA review team.

Date	To	From	Description
05/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Fax: Response to division's request for EPIX to provide questions for the June 5, 2008 T-con
05/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Previously submitted with regard to the June 5, 2008 T-con
06/04/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Division's fax of draft responses and comments to questions from EPIX in preparation for the T-con scheduled for June 5, 2008 with regard to NDA 21-711 re-submission
06/04/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: 2 additional attendees for June 5, 2008 T-con with Division regarding NDA Resubmission. Shahidah Muhammad and Rebecca Warwick
06/06/2008	James Moore, FDA	Margaret Uprichard, EPIX	Mail: EPIX attendee list sent to the Division with Request for Division's attendee list, regarding the June 5, 2008 NDA Resubmission T-con
06/10/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Response to EPIX's question: Has the Division issued a Pediatric Waiver and if Division would prefer to Receive the request as part of the NDA Resubmission.
06/11/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Division's confirmation response with regard to Dr. Rieves no longer serving as "acting" Division Director but is now the "Division Director."
06/13/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX's minutes from the June 5, 2008 T-Con, requested by the Division
06/16/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: From the Reviewing Chemist, with regard to the NDA 21-711 scheduled resubmission

Date	To	From	Description
06/26/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Maggie's email notifying the Division that the NDA Resubmission for Vasovist will be submitted on Monday, June 30, 2008, 2 weeks ahead of the scheduled given date
07/01/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: Notification that the NDA Resubmission Package was sent and delivered via FedEx from EPIX to the Division's document room
07/02/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Division's meeting minutes from the T-con
07/16/2008	James Moore & Kyong Kang, FDA	Margaret Uprichard, EPIX	Email, Fax: Copy of the NDA Resubmission Index and Cover Letter. Inquiry made on status of Acknowledgement of Receipt Letter
07/17/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX request for an update on the Acknowledgement of receipt letter for the Vasovist® NDA Resubmission including the classification and review goal date
07/18/2008	James Moore, FDA	Maggie Uprichard, EPIX	Email: Status of FDA Acknowledgement of Receipt letter for the Vasovist® NDA Resubmission
07/23/2008	Margaret Uprichard, EPIX	James Moore, FDA	Email: Division's email verification that the Acknowledgement letter for the NDA 21-711 Vasovist® Resubmission will be signed and faxed no later than 07/24/2008
07/24/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Division's Acknowledgement Letter of the NDA 21-711 Vasovist® Resubmission dated June 30, 2008, with a Class 2 response to the November 21, 2005 action letter. The user fee goal date is set for December 31, 2008.

Date	To	From	Description
09/23/2008	Margaret Uprichard, EPIX	James Moore, FDA	Fax: Division's fax for EPIX to confirm if the datasets requested by Dr. Anthony Mucci were cited in the NDA Resubmission of June 30, 2008
09/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email: EPIX confirmed that the datasets cited and included in the NDA Resubmission (June 30, 2008) are the datasets requested by Dr. Anthony Mucci
09/23/2008	James Moore, FDA	Margaret Uprichard, EPIX	Email, Phone: EPIX's Response to Division's phone message requesting the address of the core imaging facility that conducted the re-read as well as confirmation of received fax